Great Expectations:

The Impact of Autism and Alexithymia on Pain Perception



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Chapter 2 The study was designed by Geoffrey Bird and Eri Ichijo. This chapter is comprised of several studies, with various data collection methods. Study 1 data are all publicly available data sets collected on national and international level from the UK Data Service. Study 2 data collection was carried out by Katerina Vafeiadou, as part of the TOUCH study conducted by Michael Banissy's team. Study 3 and 4 data collection was led by Eri Ichijo and Mirta Stantić, in collaboration with Georgina Jefferson as well as with Firat Caglar (Study 3), and Isabel De Castro (Study 4). Eri Ichijo led the data analysis, in collaboration with Ka-Shu Lee.

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List of Abbreviations

aut+alex	Autism with alexithymia group
aut-alex	Autism without alexithymia group
alex	Alexithymia without autism group
nt	Neurotypical group
ADOS-2	Autism Diagnostic Observation Schedule (Second Edition)
AQ-50	Autism Spectrum Quotient Questionnaire
BDI-II	Beck Depression Inventory
BPQs-A	Body Perception Questionnaire (Short Form), Awareness sub-scale
DASS-21	Depression, Anxiety and Stress Scale - 21 Items
GHQ-12	12-item General Health Questionnaire
IAS	Interoceptive Accuracy Scale
IATS	Interoceptive Attention Scale
IUS-12	Intolerance of Uncertainty Scale (Short Version)
PCS	Pain Catastrophising Scale
STAI-1	Spielberger State/Trait Anxiety Inventory, State
STAI-2	Spielberger State/Trait Anxiety Inventory, Trait
PHQ-8	8-item Patient Health Questionnaire
TAS-20	20-item Toronto Alexithymia Scale
WASI-II	Wechsler Abbreviated Scale of Intelligence (Second Edition)
MR	Matrix Reasoning sub-scale of the WASI-II
FSIQ	Full Scale Intelligence Quotient
WEMWBS	Warwick-Edinburgh Mental-Wellbeing Scale
WHO-5	The World Health Organization Well-Being Index

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Abstract

Pain is a multi-faceted psychological concept, having sensory, affective, motivational, and cognitive aspects. It is an interoceptive signal, one that alerts the person of actual or potential tissue damage that needs to be eliminated. Expectation is one of the cognitive modulators of pain perception, resulting in well-established phenomena such as placebo effects, where the expectation of pain relief attenuates the perception of pain intensity. Atypical sensory sensitivity is one of the diagnostic criteria in autism, a highly heterogeneous neurodevelopmental condition. Studies on pain perception in autism have repeatedly found mixed results, and studies investigating the cognitive modulation of pain in autism are limited. Furthermore, few take into account individual differences within the autism spectrum. This thesis seeks to fill these gaps in research on cognitive modulation of pain, in particular, modulation of pain by expectation, in autism, while taking individual differences in autistic and non-autistic (particularly alexithymic) traits into account.

Chapter 1 provides a general overview of pain, and autism. Theoretical frameworks applied in the empirical chapters, such as cognitive accounts of pain perception, the Bayesian account of autism, and the alexithymia hypothesis, are outlined and reviewed.

Chapter 2 compares sub-clinical levels of mental health symptoms in the general population and a typical psychology study participant pool. This chapter aimed to assess the prevalence of common mental health traits in psychology volunteers compared to the general population, and whether these symptoms, even at sub-clinical level, could affect standard cognitive tasks. Results showed that there are sub-groups within our psychology volunteers, who all showed elevated levels of mental health symptoms compared to the general population. There were also significant differences in cognitive task performance between these sub-groups.

Chapters 3 and 4 investigate the effect of expectation on pain perception, where expectations are presented in the form of a cue and are of fixed values. In Chapter 3, a placebo hypoalgesia paradigm is employed to assess whether the magnitude of the placebo effect (i.e., how much expectation is incorporated into perception) is modulated by either autistic or alexithymic traits. Results showed it is alexithymic traits, not autistic traits, that predict the magnitude of the initial placebo effect. In Chapter 4, the effect of prediction error size and valence on pain perception is investigated using a novel prediction error size paradigm. Results showed that, in line with the previous study, the magnitude and the valence of prediction error impacted pain perception. Autism modulated this effect, while alexithymia modulated how this effect changed over the course of the task.

Chapter 5 investigates the effect of expectation on sensory perception using probabilistic cues. Two experiments, one using pain stimuli and another using visual stimuli, are conducted to assess whether the effect of autism or alexithymia on cue integration, if any, is limited to the interoceptive domain, or can also be observed in the exteroceptive domain. Results showed no effects of autism or alexithymia, though the matter remains unclear due to an observed ceiling effect.

Chapter 6 discusses the findings of this thesis in a wider context, and its implications in the field of pain, autism, and alexithymia research.

Chapter 1

Introduction

1.1 Pain

Much is known about the role of pain in directing attention to injury and potential tissue damage. Yet, there remain many unknowns regarding the cognitive mechanisms underlying pain perception and the wider functions of pain. Pain experience is fundamentally a subjective one, and its definition, despite it being central to our everyday lives, remains a hotly debated topic (Anand & Craig, 1996; Aydede, 2019). According to the International Association for the Study of Pain (IASP), who recently revised its definition, pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020, p. 1977). Pain, therefore, is a multi-dimensional psychological concept, that is distinguishable from a physical state (Merskey, 1994). It cannot be inferred just from the activity in sensory neurons as a result of nociceptive input, for example (Raja et al., 2020).

Pain is not the same as nociception, and pain and nociception can exist without each other (Loeser & Treede, 2008). Nociception is defined as the physiological encoding and processing of nociceptive stimuli (Ledowski, 2019). If pain were the same as nociception, then there would be a direct correlation between the delivered intensity of stimulation and reported pain intensity. For example, application of a voltage of 5 mA to the skin would always be rated as producing a consistent degree of pain. However, the observation of offset analgesia, a phenomenon in which a disproportionately large decrease in pain intensity rating is observed following a small

decrease in the delivered intensity, demonstrates that the relationship between nociception and pain is not linear and the phenomenon of placebo hypoalgesia (see Section 1.1.2) demonstrates that the mapping between stimulation intensity and experienced pain is not consistent across time or contexts (Ligato et al., 2018; Petersen et al., 2018).

1.1.1 Pain and Interoception

Pain is almost never a motivationally neutral signal, as it alerts the person of actual or potential tissue damage that needs to be eliminated, and thus of the need to regain homeostasis (Craig, 2002; Fields, 2018). It has sensory, affective, motivational, and cognitive aspects, and is an interoceptive signal (Craig, 2002). Interoception refers to the perception of internal states of the body, such as heart beats and thirst (Craig, 2002; Sherrington, 1907). Several interoceptive signals, for example, hunger, also have sensory, motivational, affective, and associated cognitive aspects (Stevenson et al., 2015).

Neuroimaging studies of pain have shown activation of cortical regions seen using interoceptive stimuli, such as the insula and the anterior cingulate cortex (ACC), which are activated by temperature, pain and other interoceptive modalities, such as hunger (Craig, 2002; Wager et al., 2013). Studies have shown that sensory information is transmitted to the anterior insular, somatosensory and orbitofrontal cortices, areas which support the perception of a range of states, such as those generated by bodily organs (e.g., heart, stomach; Critchley et al., 2004; Khalsa et al., 2009; Starr et al., 2011). The posterior insula is argued to be the region containing the primary interoceptive cortex (Failla, Bryant, et al., 2020), whereas the anterior insula and the ACC are thought to provide a secondary representation implementing the conscious sense of the bodily self (Huang et al., 2021). The anterior insula is thought to be part of brain networks associated with self-related cognition or externally and internally oriented attention processes (W. Li et al., 2023). Activation of the ACC in particular, has been found to be directly correlated with the unpleasantness of thermal pain (Rainville et al., 1997).

However, an fMRI study of stroke patients with a complete destruction of both the insulae and ACC, but with bilaterally intact primary somatosensory cortex, showed they could rate pain

typically and interoception was also still intact (Feinstein et al., 2016). This result suggests that the insulae and ACC may not be necessary for interoceptive accuracy (Damasio et al., 2013; Feinstein et al., 2016; Khalsa et al., 2009). Although these patients were able to detect pain, their pain experience was atypical: in a cold pressor task, one patient's pain tolerance threshold was significantly lower than a group of control participants' average pain threshold, and exhibited extreme pain intensity ratings (Feinstein et al., 2016). Describing their pain experience as being intact may not be an accurate depiction, though it cannot be known how typical their pain perception prior to the strokes were. This also points to the complexity of interoception, which is argued to have four facets: objective and subjective measures of both accuracy and attention (Murphy et al., 2019). It may be that subjective interoceptive accuracy is unimpaired even when the insulae and ACC are destroyed, but it is not yet known whether objective interoceptive accuracy is unaffected.

1.1.2 Pain and Expectation

The cognitive aspects of the pain experience are essential to consider, and are central to this thesis. The subjective experience of pain is modulated by cognitive factors such as attention, reappraisal, and agency (Villemure & Bushnell, 2009; Wiech, 2023; Wiech et al., 2008; A. Williams & Craig, 2016). One cognitive factor that influences pain perception, which will be the focus on this thesis, is expectation (Fields, 2018).

The influence of expectation on pain perception has been studied extensively, with well-known phenomena such as placebo (Au Yeung et al., 2014; Colloca & Benedetti, 2006; Colloca et al., 2013) and nocebo effects (Benedetti et al., 2006; Colloca & Benedetti, 2007; Manaï et al., 2019; Reicherts et al., 2016). Placebo and nocebo effects are examples of cognitive pain modulation, where expectations about upcoming pain can either attenuate (i.e., placebo hypoalgesia), or amplify (i.e., nocebo hyperalgesia) pain (Colloca & Benedetti, 2006; Wiech et al., 2008). Expectation of upcoming pain can be built through conditioning (Colloca et al., 2010) and verbal instructions, with verbal instructions alone sufficient to cause a change in behavioural (Pollo et al., 2001) and neural (Rodriguez-Raecke et al., 2010) pain responses.

The influence of expectation on sensory perception, as in top-down effects of expectation, can be understood in the context of a Bayesian perceptual framework. Within Bayesian frameworks, the brain has a model of the world (i.e., expectations) that it continuously tries to optimise using sensory inputs (i.e., sensory evidence; Friston, 2010). The model of the world is built by incorporating prediction errors (the discrepancy between the expectation and sensory evidence), and updating expectations accordingly. Understanding perception using such a framework has been supported mostly in vision (Kok et al., 2013; Summerfield & de Lange, 2014), but also in interoception (Seth et al., 2012), and in particular, pain (Hird et al., 2019; Song et al., 2021; Wiech et al., 2014). A simple schematic overview of the Bayesian framework is shown in Figure 1.1.

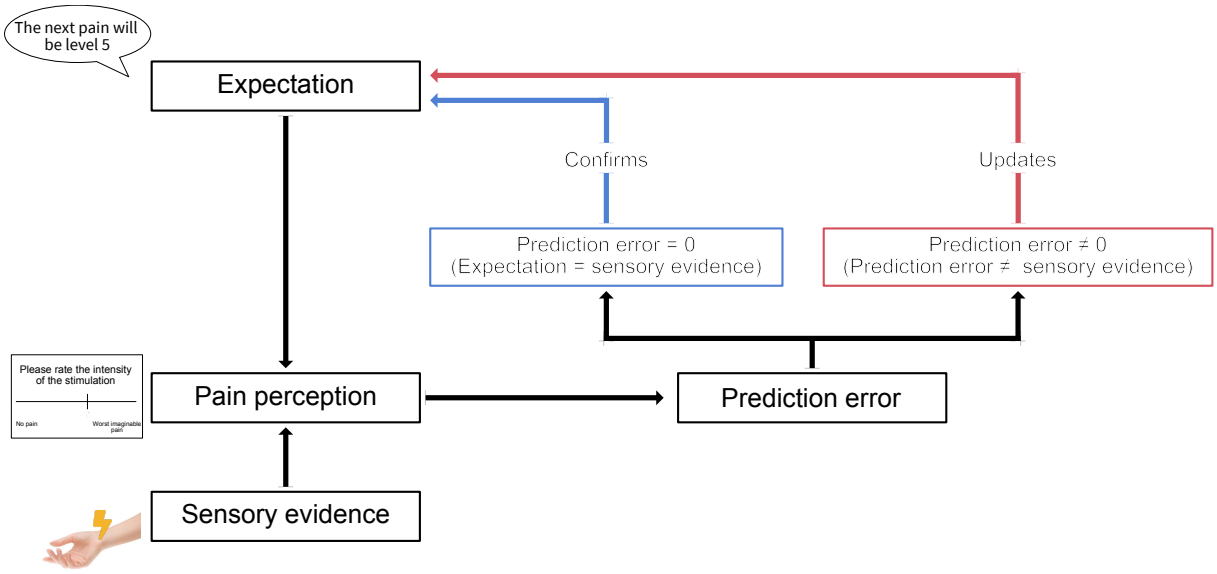


Figure 1.1: Influence of expectation on pain perception. Top-down expectations about upcoming painful stimuli are generated, and combined with the bottom-up sensory evidence. These two components are weighted (according to their precision) to form a percept. If there is a prediction error (i.e., discrepancy between expected and delivered stimulus intensity), then the expectation is updated. Otherwise, the expectation is confirmed, and its precision increased.

The extent to which expectation, and sensory evidence, are incorporated into perception is dependent on their precision. If the precision of a component is high, then that component is weighted more in pain perception (Büchel et al., 2014). If the precision of expectation is high, then pain perception will be influenced greatly by expectation, and varying the precision of expectation via verbal instructions can elicit different placebo effect sizes (Pollo et al., 2001). Studies where cues of varying precision were presented showed that probabilistic cues (higher

uncertainty, lower precision) when compared to deterministic cues (lower uncertainty, higher precision), lead to an increased effect on pain intensity ratings (Brown et al., 2008; Lin et al., 2014). This is in line with cancellation theories, where studies have found lower sensory cortical activation when sensory inputs are predictable, as well as them being perceived as less intense than unexpected inputs (S. Becker et al., 2021; Press et al., 2020). Evidence is not fully supportive of this idea, however, as two studies using a similar paradigm with uncertain cues found discordant results. Uncertain cues led to higher pain ratings (Yoshida et al., 2013), possibly via their effect on expectations, as well as pain ratings being unaffected by uncertainty (Zaman et al., 2017). However, there are limits to how much expectation can influence pain perception; when sensory evidence is greatly different to what was expected (i.e., a large prediction error), then the influence of expectation is reduced (Hird et al., 2019).

1.1.3 Pain and Individual Differences

Another aspect of pain experience that needs to be considered is the effect of individual differences in personality traits and mental health conditions that impacts pain perception. For example, people who are in the acute phase of disordered eating, a condition marked by dysfunctional interoceptive processing, have been found to have increased pain tolerance (Bär et al., 2013; Yamamotova et al., 2009).

Studies on emotional modulation of pain, whereby pain intensity ratings decrease when viewing positively-valenced emotional stimuli, and increase when viewing negatively-valenced emotional stimuli, suggest that manipulating the affective part of pain experience can alter the sensory perception of pain (McIver et al., 2018). Moreover, it was found that the magnitude of the emotional modulation was influenced by anxious and depressive traits: the greater the depressive symptoms, the bigger the influence of negative emotion on pain perception, and the greater the state anxiety symptoms, the lesser the effect of emotion modulation on pain perception (McIver et al., 2018). These results support studies that report anxiety (Bair et al., 2013) and depression (Castillo et al., 2013) effects on pain perception.

Anxiety-induced hyperalgesia has been shown to increase perceived pain intensity (Colloca

& Benedetti, 2007). Indeed, nocebo-induced hyperalgesia was blocked with an administration of an anti-anxiety drug diazepam, a benzodiazepine, with the baseline pain level remaining unchanged (Benedetti et al., 2006). However, anxiety can either amplify or attenuate pain depending on where the anxiety is directed to. Anxiety about pain amplifies pain perception, but anxiety about the environment (e.g., presence of a stressor) attenuates pain, once again showing the importance of cognitive modulation of pain (Benedetti et al., 2006; Colloca & Benedetti, 2007).

The tendency to catastrophise pain is another important individual difference to consider. Pain catastrophising is marked by the tendency to magnify the threat value of the pain, to feel helpless and be unable to manage pain-related thoughts when anticipating, receiving, or following the pain event (Petrini & Arendt-Nielsen, 2020). Hypervigilance of somatic sensations is often observed in those with anxiety and panic disorders, and panic disorder patients are more likely than non-panic disorder patients to interpret bodily sensations as precursors to a catastrophic event (e.g., heart attack, insanity; Petrini & Arendt-Nielsen, 2020). Furthermore, negative emotions have been shown to intensify or lead to catastrophic misinterpretation of physical arousal in anxiety and panic disorders (Teachman et al., 2010). These results suggest how tendencies to be hypervigilant, experience negative affect, and misinterpret somatic sensations, could lead to catastrophising of pain signals.

These effects of individual differences are in addition to the effects of personality traits, such as dispositional optimism (Morton et al., 2009), suggestibility (De Pascalis et al., 2002), agreeableness and resilience (Peciña et al., 2013), which have been shown to explain a significant proportion of variance in behavioural placebo hypoalgesic response. Furthermore, Peciña et al. (2013) showed that those scoring above the median in these personality traits had greater placebo-induced activation of the dorsal ACC.

It can be seen that there are many factors which impact upon the experience of pain, which as far as possible need to be accounted for in studies of pain. This thesis is particularly concerned with pain processing in autism, and this condition will be discussed next.

1.2 Autism

Autism is a spectrum of neurodevelopmental conditions characterised by difficulties across social, perceptual, and behavioural domains (American Psychiatric Association, 2013). Indeed, while autism is typically associated with difficulties in social interactions and communication, there is a growing scientific consensus that atypical reactivity to sensory input is as central a feature of autism. Examples include hypersensitivity to visual and auditory stimuli (Marco et al., 2011), and apparent indifference to pain/temperature (American Psychiatric Association, 2013; Moore, 2015). (Note: In what follows, the word "autistic" is used to refer to individuals with autism as this terminology is preferred by the autistic community; Keating et al., 2023).

Recently, researchers have suggested that the atypical perception observed in autism can be explained by differences in Bayesian Inference, where autistic perception is shaped more by sensory inputs, rather than expectations (Brock, 2012; Lawson et al., 2014; Pellicano & Burr, 2012; Sinha et al., 2014; Van de Cruys et al., 2014). This could be due to decreased precision of priors, or increased precision of sensory evidence, or difficulties in modulating precision of Bayesian components (prior, sensory evidence, prediction error, etc) depending on the context (Cannon et al., 2021). The Bayesian account of autism has the potential to explain significant autistic behavioural traits: atypical sensory perception, and restricted and repetitive behaviours (American Psychiatric Association, 2013). Perception dominated by sensory inputs would hinder prioritisation of multiple incoming sensory inputs, resulting in atypical sensory experience, such as decreased susceptibility to sensory illusion as explained by the weak central coherence account (Happé & Frith, 2006).

One of the characteristics observed in autism is intolerance of uncertainty, which is the tendency to react negatively to uncertain situations (Buhr & Dugas, 2009; South & Rodgers, 2017). Intolerance of uncertainty would lead to behavioural adaptations designed to minimise surprise, such as repetitive behaviour, as a way to reduce the uncertainty caused by weak priors. Although the Bayesian account of autism has wide explanatory power for the symptoms of autism, recent studies investigating the Bayesian account of autism have found mixed results, even when limiting the studies to those investigating sensory perception. Some have found

weaker influence of expectation or greater sensory precision on perception in autistic people than in neurotypical people (Goris et al., 2018; Karvelis et al., 2018; Lawson et al., 2017; Lieder et al., 2019; Van Boxtel et al., 2016), while other studies have found no group differences (Karaminis et al., 2020; Manning et al., 2017; Tewolde et al., 2018; Van de Cruys et al., 2018). The inconsistent findings could be due to a lack of consideration of heterogeneity in autism. The studies fail to consider potential covariates, such as anxiety, the prevalence of which is found to be higher in autistic adults than in non-autistic adults (South & Rodgers, 2017). Furthermore, no study has yet studied the Bayesian account of autism using pain stimuli.

1.2.1 Autism and Pain

Pain experience in what follows refers to acute pain induced by sensory inputs (e.g., heat, electricity, etc), rather than social context (e.g., social rejection, empathy for pain). Studies of pain in autism have resulted in mixed, even contradictory, findings: studies have found typical pain thresholds (Bird et al., 2010; Failla, Gerdes, et al., 2020; Z. J. Williams et al., 2019; Yasuda et al., 2016), decreased pain sensitivity (Yasuda et al., 2016), increased pain sensitivity (Dubois et al., 2020; Hoffman et al., 2022), typical pain sensitivity (Failla et al., 2018), greater intra-individual variability (Dubois et al., 2020; Failla et al., 2018; Failla, Gerdes, et al., 2020; Vaughan et al., 2020), and attenuated (Chien et al., 2017), increased (Gu et al., 2018), and atypical pattern of neural responses (Failla et al., 2018) to pain in autistic individuals compared to neurotypical individuals.

Pain perception studies in autism often focus on behavioural and neural correlates of pain detection and tolerance thresholds (Chien et al., 2017; Failla et al., 2018). The vastly inconsistent results in the field, in part, could be explained by the differences in pain expression (Kalingel-Levi et al., 2022; Nader et al., 2004) and verbal reporting (Thong et al., 2018), due to measurement of pain that has not been tailored to the autistic population.

It should also be noted that the method of pain induction varies between experiments. While some use heat (Chien et al., 2017; Failla et al., 2018; Failla, Gerdes, et al., 2020; Z. J. Williams et al., 2019), others use electrical stimuli (Bird et al., 2010). Quantitative sensory testing, which

involves a battery of tests with various pain induction methods, such as cold (pain) detection threshold, mechanical (pain) detection threshold, has found non-systematic group differences between autism and non-autism groups (Fründt et al., 2017; Vaughan et al., 2020). However, Yasuda et al. (2016) found consistently decreased pain sensitivity across three pain modalities of electricity, heat, and cold in autism. Moreover, a study by Hird et al. (2018) on neurotypical participants showed that pain-related event-related potentials were modulated equivalently by expectation of both laser and electric stimulation. These results suggest that differences in pain induction may explain some, but not all, of the variance in the results of studies. Thus, even after accounting for these effects, there is still substantial unexplained heterogeneity in the results of studies testing pain processing in autism.

There are limited number of studies on the influence of cognitive mechanisms, such as expectation, on pain perception in autism. Gu et al. (2018) found differences in the neural response to anticipation of pain (within dorsal ACC) in autism, but not to pain stimulation. However, this study recruited only male autistic individuals, and collected behavioural pain intensity rating at the end of every block, rather than at every trial. One of the aims of this thesis is to fill this gap in research, by using the Bayesian framework of pain perception and to test the Bayesian account of autism.

Moreover, only a small number of the pain studies in autism take individual differences, such as depressive and anxious traits, into account (Dubois et al., 2020; Failla, Gerdes, et al., 2020). Autism is a highly heterogeneous condition with many autistic individuals having co-occurring mental health conditions (Lai et al., 2019). A recent study on children with autism and their siblings without autism showed that autistic children had substantially higher standardised prevalence of all comorbidities analysed in the study, including anxiety, attention deficit hyperactivity disorder (ADHD), depression, and obsessive compulsive disorder (OCD; Khachadourian et al., 2023). In particular, it can be argued that considering variance in alexithymic traits could be key when looking at individual differences in perception in autism, especially in the interoceptive domain such as pain. This is because research suggests that it is alexithymic traits, not autistic traits, that are responsible for atypical interoception when it occurs in the autistic population (Brewer et al., 2015).

1.2.2 Autism and Alexithymia

Alexithymia is a sub-clinical condition characterised by difficulties in identifying one's own emotions and distinguishing bodily sensations from emotions (Nemiah, 1977). It co-occurs with a range of psychiatric conditions, such as eating disorders (Nowakowski et al., 2013), substance misuse (Taylor et al., 1990), anxiety (Berthoz et al., 1999; Marchesi et al., 2000), depression (Leweke et al., 2012; S. Li et al., 2015), and OCD (Grabe et al., 2006). Alexithymia affects up to 50% of the autistic population, but only 5% of the general population (Kinnaird et al., 2019).

Recent studies suggest that alexithymia stems from general interoceptive difficulties (Brewer et al., 2016; DuBois et al., 2016; Murphy et al., 2018). Li et al. (2023), in their longitudinal study, reported that changes in alexithymic traits were correlated with changes in insular grey matter volume, a brain region shown to be implicated in interoception. In the context of clinical symptoms, in panic disorders, for example, alexithymia was found to be related to somatosensory amplification (De Berardis et al., 2007). In the context of pain, Pollatos et al. (2015) found that alexithymia was associated with higher pain tolerance, while Nyklíček et al. (2000) found alexithymia to be associated with lower pain tolerance.

Studies have shown that interoceptive difficulties observed in autism are better explained by the co-occurring alexithymia rather than autism itself (Cuve et al., 2021; Gaigg et al., 2018; P. Shah et al., 2016). This will be referred to as the alexithymia hypothesis (Brewer et al., 2015). Atypical interoception has been suggested to be a candidate for the p-factor, a factor which has been suggested to represent one's risk for developing and maintaining psychiatric conditions, which accounts for common symptoms and co-occurrence between psychiatric conditions (Murphy et al., 2017). This potential implication makes it important to study alexithymia not only for its impact within the autism community, but for the wider population of those who are affected by various psychiatric conditions.

The alexithymia hypothesis has relevance for the application of the Bayesian account of autism to pain perception in autism. As an interoceptive signal, within the autistic population, it may be alexithymia, not autism, that is responsible for i) atypical pain perception, and ii) the effects of expectation on pain processing. Given that approximately 50% of the autistic

population are alexithymic (Kinnaird et al., 2019), sampling variance with respect to alexithymia could also explain the mixed results of studies investigating pain perception in autism. If a sample of autistic individuals happens to contain a large amount of alexithymic individuals, then the autism group's pain perception may appear atypical. If the sample mostly contains non-alexithymic individuals, then the autism group's pain perception may be typical. Thus, under this account, any increased precision of sensory evidence of interoceptive signals is driven by alexithymic traits, rather than autistic traits.

No study has used pain, an interoceptive signal, to test the alexithymia hypothesis in autism in the context of the Bayesian account of autism. Additionally, no study has studied the cognitive modulation of pain in alexithymia. One of the aims of this thesis is to fill these gaps in research, by applying the alexithymia hypothesis within the Bayesian account of autism in the context of pain perception.

1.3 Aims of the Thesis

The overall goal of the thesis is to gain a better understanding of any differences in the effect of expectations on pain perception between autistic and non-autistic people. The three main theories that will be tested are i) the cognitive modulation of pain perception (Wiech et al., 2008), ii) the Bayesian account of autism (Pellicano & Burr, 2012), and ii) the alexithymia hypothesis (Brewer et al., 2015). Given the highly heterogeneous nature of autism, and how pain experience can be modulated by many traits, all four empirical chapters collect self-report measures of common mental health traits in an attempt to control for confounding variables. Chapter 2 is an empirical chapter focusing on psychological studies of mental health to identify whether neurotypical control groups are homogeneous and free from psychiatric symptoms, while Chapters 3 through 5 are empirical chapters on pain perception in autism and alexithymia.

Chapter 2 investigates whether the neurotypical groups used in psychology studies have higher mental health traits than the general population. A series of studies assess whether a typical psychology testing sample, compared to the general population, has higher mental health traits that are often not controlled for in psychology experiments. And if so, whether there is a

need to control for common mental health traits in the experiments that follow in the thesis.

Chapter 3 reports on a study designed to determine whether the influence of expectation on pain perception is modulated by autistic and alexithymic traits. It uses a placebo hypoalgesia paradigm in which expectations of pain relief were reinforced through conditioning and verbal instructions, allowing participants to build precise priors about upcoming pain stimuli. The aim of this experiment was to assess whether the magnitude of the placebo effect, which is dependent on the precision of the prior built during the conditioning phase, is influenced by autistic or alexithymic traits.

Chapter 4 studies whether prediction error size and valence modulate the effect of priors on pain perception. A novel prediction error size paradigm was used to elicit varying magnitudes and valence of prediction error. The aim of this experiment was to assess whether prediction error size and valence affect pain perception, and if so, whether these effects are influenced by autistic or alexithymic traits.

Chapter 5 investigates the effect of probabilistic cues on perception, and compares the alexithymia effect in interoceptive and exteroceptive domains. Two experiments using the same probabilistic cueing paradigm in two different domains, interoception (pain) and exteroception (vision), were conducted. The aim of this experiment was to test whether the alexithymia hypothesis applies only to the interoceptive domain, and to test whether the differences in the expectations built during the task are modulated by autistic or alexithymic traits.

The thesis as a whole aims to further our understanding of the role of expectation on pain perception in the autistic and alexithymic population. Moreover, it aims to contribute to the literature investigating the Bayesian account of autism and the alexithymia hypothesis in the context of pain, a domain of perception under-researched in autism more generally.

Chapter 2

Effects of mental health traits on cognitive tasks: the influence of biased sampling

Abstract

One of the continuing challenges of psychological research is obtaining a sample that is representative of the general population. One largely overlooked participant characteristic is sub-clinical levels of mental health symptoms, such as anxiety and depression. A series of studies were conducted to assess i) whether typical volunteers for psychology studies had more mental health symptoms than the general population, ii) if there are sub-groups within the no-diagnosis, no-medication participant pool, and iii) whether sub-clinical levels of mental health symptoms have an effect on standard behavioural tasks (Stroop, n-back, matrix reasoning). Results showed that when compared to the national data sets, volunteers showed higher levels of mental health symptoms. Latent profile analysis revealed that there are sub-groups within our neurotypical participant group, characterised by mental health symptoms, which resulted in a five-profile solution. Furthermore, these latent profiles were found to have an effect on some of the behavioural task performance outcomes. This study offers empirical evidence of the need to measure and control for mental health symptoms, including minor sub-clinical levels of mental health symptoms. Such symptoms, even in participants who do not have psychiatric diagnoses or take psychotropic medications, can have significant effects on standard behavioural tasks.

2.1 Introduction

The reproducibility crisis is currently gaining attention in psychological science (Open Science Collaboration, 2015). Statistical power, selective reporting, and various aspects of between-study heterogeneity have been suggested as some of the possible factors contributing to the crisis (Stanley et al., 2018). One aspect of between-study heterogeneity that receives less attention than it perhaps should is the problem of selecting an appropriately representative sample of participants from the general population. As psychological research relies on voluntary participants, it inevitably results in unrepresentative sampling, for instance, a skewed representation of demographic factors such as age and socio-economic status (Nielsen et al., 2017). In order to account for skewed sampling and its possible effects on outcomes of studies, information on demographic variables (typically age and gender, and sometimes ethnicity) is collected and controlled for statistically. Reassuringly, a recent study found that the reproducibility crisis is mostly explained by statistical limitations of studies, rather than biased sampling with respect to these factors (Klein et al., 2018).

However, it is likely that the participant pool for psychology studies is not representative solely in demographic variables like age and socio-economic status, but also in the prevalence of sub-clinical levels of mental health symptoms. Participants often consist of populations who have been reported to have more mental health symptoms, such as university students (Office for National Statistics, 2020), and casually-employed people (Buckman et al., 2022), who are attracted to the quick financial compensation and no working-hour restrictions. While the rise in popularity of online studies has allowed researchers to overcome the geographical and working-time constraints associated with on-site testing, online testing has its own challenges: constraints with respect to availability of computers and fast internet, or biased sampling with respect to those participants who see and respond to advertisements.

Many psychology studies recruit people with no current or recent psychiatric diagnoses and who are not currently taking or have recently taken psychotropic medications, in an attempt to remove any effects of clinical levels of mental health conditions. Yet, lack of diagnosis does not equate to absence of symptoms. While mental health diagnoses are binary (one either has

or does not have a diagnosis), symptoms exist along a continuum (Crawford et al., 2011; Löwe et al., 2008). A primary issue is that mental health symptoms tend to be viewed as discrete variables; researchers often use variously arbitrary cut-offs that promote a binary healthy/not healthy classification. This is not reflective of the reality of various mental health conditions. In addition, appropriate cut-offs differ across age groups and clinical populations (Castro-Costa et al., 2007; Julian, 2011; White et al., 2009). Mental health symptoms, even at sub-clinical levels, are known to affect cognitive abilities (Segal et al., 2015; Thoresen et al., 2016). It is therefore likely that mental health symptoms should be measured and controlled for, even in standard behavioural tasks with no ostensive clinical focus.

2.1.1 Goals and Hypotheses

Several studies were conducted to assess the prevalence of mental health symptoms in participants who would typically be considered members of a neurotypical comparison group in psychological studies, as they do not have mental health diagnoses and do not take any psychotropic medications. The aims of this study were three-fold. First, to investigate whether our pool of psychology study participants has more mental health symptoms compared to participants from national data sets, representative of the general population. Second, to assess whether our participants were truly neurotypical (i.e., minimal mood symptoms), or whether the pool consisted of various sub-groups characterised by the presence of symptoms of mental health conditions through latent profile analysis (LPA). Such a finding would suggest that the present assumption that "neurotypical psychological research volunteers" comprise one homogeneous group is false. And third, to determine whether performance in standard cognitive tasks differs depending on the mental health profile of volunteers. It was hypothesised that compared to the national data sets, our participants would have more mental health symptoms as measured by commonly-used self-report questionnaires, based on pilot data (Ichijo et al., 2019). Additionally, it was hypothesised that variabilities in mental health symptoms in our participants would be reflected in multiple sub-groups, and have an effect on performance on standard behavioural tasks that use purely cognitive stimuli.

2.2 Methods

2.2.1 Participants

To best replicate the standard practice of recruiting and/or identifying neurotypical participants in the field, for all studies, participants were first included if they: i) were aged between 18 to 65 years old, ii) had no psychiatric diagnoses, and ii) did not use psychotropic medications at time of study administration or six months before. Critically, where information was available, exclusion criteria were applied carefully to participants who i) identified themselves as neurodiverse (i.e., formal/informal/self-diagnoses of autism, and ADHD) , ii) had other health issues (e.g., vision, mobility), and iii) had incomplete demographic data or responded with "Prefer not to answer" or "Other" to any of the exclusionary items stated above. Finally, only UK-based participants were included. This was due to the consideration that our primary data collection took place amid the COVID-19 pandemic, and that focusing on UK participants would ease the interpretation of results by removing pandemic-related variances (e.g., different public health restrictions), which might differ in participants from other countries.

Table 2.1 summarises the study sample sizes at various stages of applying the exclusion criteria.

Table 2.1: Participant exclusion process. Exclusion criteria were as follows. i) Removal of non-UK data. For Study 2, this also included participants who completed the study after the start of the national lockdown in the UK due to COVID-19. ii) Removal of data with less than 80% of questionnaire responses completed. Final sample refers to the number of participants who met the inclusion criteria, resulting in the final study sample for subsequent analyses.

Data set	Year	Questionnaire and tasks	Initial sample	Exclusion criteria i	Exclusion criteria ii	Final sample
EQoLS	2011	WHO-5	142,435	6,075	5,048	2,544
EHIS	2013	PHQ-8	20,161	20,161	17,846	7,945
HSE	2016	GHQ-12	10,067	10,067	7,300	1,804
		WEMWBS	10,067	10,067	7,067	1,803
HSE	2018	GHQ-12	10,250	10,250	7,606	1,729
HSE	2019	WEMWBS	10,299	10,299	7,457	1,798
Study 2	2020	WEMWBS-7	43,094	23,741	23,687	11,807
Study 3	2020	BDI-II, STAI-1, STAI-2, DASS-21, GHQ-12 PHQ-8, WEMWBS, WHO-5	872	664	494	494
Study 4	2020-2022	BDI-II, STAI-1, STAI-2, DASS-21, PHQ-8 WEMWBS, Stroop, n-back, matrix reasoning	267	227	223	223

Study 1

To ascertain nationwide levels of mental health symptoms/well-being as references to compare with our primary neurotypical groups (Studies 2-3), multi-stage stratified random control samples were obtained via the UK Data Service (https://ukdataservice.ac.uk/). These secondary data sets were selected based on five criteria: i) large sample size (N > 10,000), ii) data collected between 2010 to 2020, iii) standardised measures of mental health symptoms and well-being, iv) availability and quality of screening questions that allow for classifying participants as neurotypical participants, and v) free data access. This resulted in five secondary data sets for our analyses: The European Quality of Life Survey (EQoLS, 2011), United Kingdom data of The European Health Interview Survey (EHIS, 2013), and Health Survey for England (HSE, 2016, 2018 and 2019).

As is typical with nationwide secondary data sets, responses were often incomplete. To retain the largest possible sample sizes for the analyses, missing questionnaire responses were imputed using the missForest package in R (Stekhoven & Buhlmann, 2012), provided that the questionnaire responses were at least 80% complete. This threshold was determined based on the questionnaire measure with the least number of items, i.e., four out of five items on the World Health Organization Well-Being Index (WHO-5). Statistical comparison and visual inspection suggested that the means and standard deviations of the study variables were highly comparable between the original data sets and the imputed data sets ($-0.101 \leq t \leq 0.079$, all $p > .05$), with negligible out-of-the-bag (OOB) errors across data sets ($2.55 \times 10^{-5} \leq \text{OOB} \leq 4.45 \times 10^{-4}$), supporting the robustness of imputation while preserving the statistical properties of the original data sets (see Section A.1.1 for more details). After imputation, exclusion criteria (as detailed above) were applied to derive the final study samples for subsequent analyses.

Study 2

43,094 participants completed this online questionnaire study between 21st January and 1st April 2020, recruited via social media, pre-existing participant databases and local advertisements (Bowling et al., 2020). In addition to the exclusion criteria above, Study 2 responses

completed after the beginning of the first national lockdown in the UK (23rd March 2020) were excluded so as to provide a more accurate evaluation of pre-pandemic mental health symptoms in the general population. Participants completed the questionnaire measures in a randomised order on Qualtrics (Qualtrics, 2020), which took approximately 30 minutes. For the purpose of this study, only demographic information and the 7-item version of Warwick-Edinburgh Mental Wellbeing Scales (WEMWBS-7) were used.

Study 3

872 participants completed this online questionnaire study between 20th April and 31st August 2020, recruited via social media, the departmental participant recruitment system (SONA), and Prolific (www.prolific.com; Prolific, 2020). Questionnaires were completed on Gorilla (www.gorilla.sc; Anwyl-Irvine et al., 2020). The questionnaire order was randomised and the study took approximately 15 minutes to complete.

Study 4

267 participants completed this online study between 7th December 2020 and 10th November 2022, hosted on Gorilla (www.gorilla.sc; Anwyl-Irvine et al., 2020). The same recruitment strategies were used as in Study 3. The presentation order of questionnaires and behavioural tasks was randomised, and the study took approximately 35 minutes to complete.

2.2.2 Measures and Procedures

Questionnaire measures

Table 2.2 summarises the various mental health/well-being measures used in the primary and secondary data sets. While the inclusion of some of these measures was dependent on their availability in the secondary data sets, mental health measures widely used in psychological research and thus useful in evaluating mental health symptoms in our study participants were selected.

Table 2.2: Summary table of questionnaires. Total scores refer to the range of scores possible for a given questionnaire. Scores are then assigned to appropriate categories according to the total scores.

Questionnaire	Trait	No. Items	Total Scores	Categories	
				Severity	Scores
BDI-II	Depression	21	0-63	Minimal	0-13
				Mild	14-19
				Moderate	20-28
				Severe	29-63
DASS-21	Anxiety	7	0-42	Normal	0-7
				Mild	8-9
				Moderate	10-14
				Severe	15-19
				Extremely severe	20+
	Depression	7	0-42	Normal	0-9
				Mild	10-13
				Moderate	14-20
				Severe	21-27
				Extremely severe	28+
	Stress	7	0-42	Normal	0-14
				Mild	15-18
				Moderate	19-25
				Severe	26-33
				Extremely severe	34+
STAI-1 STAI-2	State anxiety Trait anxiety	20	20-80	Non-clinical anxiety Clinical anxiety	20-39 40-80
GHQ-12	Psychological morbidity	12	0-36	None	0-12
				Mild	13-15
				Moderate	16-20
				Severe	21+
PHQ-8	Depression	8	0-24	None	0-4
				Mild	5-9
				Moderate	10-14
				Moderately severe	15-19
				Severe	20+
WEMWBS	Mental well-being	14	14-70	Probable depression	0-40
				Possible depression	41-44
				Average mental well-being	45-59
				High mental well-being	60+
WEMWBS-7		7	7-35	Probable depression	0-17
				Possible depression	18-20
				Average mental well-being	21-27
				High mental well-being	28+
WHO-5	Depression	5	0-25	Poor well-being	0-13
				Well	14+

Mental health/well-being Four measures were used. The first measure was the General Health Questionnaire (GHQ-12; Goldberg & Williams, 1988), a 12-item measure used to screen common mental disorders. Each item (e.g., "Feeling unhappy and depressed") is rated on a 4-point Likert scale (0 = always, 3 = never). The second measure was the 8-item Patient Health Questionnaire (PHQ-8; Kroenke et al., 2001), which is a depression screening tool widely used in primary care settings. The PHQ-8 excludes the ninth item (suicide ideation) on the PHQ-9. Each item (e.g., "Little interest or pleasure in doing things") is rated on a 4-point Likert scale (0 = not at all, 3 = nearly every day). The third measure was the Warwick-Edinburgh Mental Wellbeing Scales (WEMWBS; Tennant et al., 2007), a 14-item measure of general mental well-being that is well-validated amongst the student and general populations. Each item (e.g., "I have been feeling optimistic about the future") is rated on a 6-point Likert scale (0 = none of the time, 5 = all of the time). A 7-item version of the WEMWBS (WEMWBS-7; N. Shah et al., 2021) was used in Study 2. The fourth measure was the 5-item World Health Organization Well-Being Index (WHO-5; World Health Organization, 1998), which measures current well-being and depressive symptoms. Each item (e.g., "I have felt cheerful in good spirits") is rated on a 6-point Likert scale (0 = at no time, 5 = all of the time).

For GHQ-12 and PHQ-8, higher scores indicate greater mental health symptom severity. For WEMWBS and WHO-5, higher scores represent better well-being. WEMWBS and WHO-5 ask participants to look back at their mental states over the past two weeks. At least one of the aforementioned measures was included in each secondary data set in Study 1 (see Table 2.1). For the primary data sets, only the WEMWBS-7 was available in Study 2, GHQ-12 and WHO-5 were available only in Study 3, whilst all other questionnaire measures were available in Studies 3 and 4. For Study 3, internal consistencies for the whole questionnaires were .888 for GHQ-12, .872 for PHQ-8, .935 for WEMWBS, and .869 for WHO-5. For Study 4, internal consistencies were .873 for PHQ-8 and .934 for WEMWBS.

Mood symptoms Four measures were used. The first two were the Beck Depression Inventory (BDI-II; Beck et al., 1996) and the Depression, Anxiety and Stress Scale (DASS-21; Lovibond & Lovibond, 1995). Both the BDI-II and DASS-21 contain 21 items rated on a 4-point Likert

scale, whereby a higher score indicates more severe symptoms (BDI-II range: 0 to 63; DASS-21 range: 0 to 21). Some example items are "I am so sad and unhappy that I can't stand it" on the BDI-II and "I couldn't seem to experience any positive feeling at all" on the DASS-21. The DASS-21 has sub-scales quantifying specific depressive, anxious, and stress symptoms (7 items each). The BDI-II asks participants about their depressive symptoms over the past two weeks. DASS-21 does not ask participants to think in terms of a time-constrained periods. These measures were available in Studies 3 and 4. In the Study 3 sample, the internal consistency for BDI-II was .894, DASS-21 depression was .872, DASS-21 anxiety was .837, and DASS-21 stress was .881. For Study 4, the internal consistency was .916 for BDI-II, .895 for DASS-21 depression, .865 for DASS-21 anxiety, and .875 for DASS-21 stress.

Additionally, Spielberger State/Trait Anxiety Inventory (STAI-1 and STAI-2; Spielberger et al., 1983) were used as measures of anxious traits. These both contain 20 items rated on a 4-point Likert scale, whereby a higher score indicates more severe symptoms (range: 20 to 80). Some examples items are "I feel calm" on STAI-1 (state), and "I am calm, cool, and collected" on STAI-2 (trait). STAI-1 asks participants how they are feeling right at the moment, while STAI-2 asks to indicate how they generally feel. Unlike other questionnaires, these two were not published with a clinical cut-off indicated, but a score of 40 is typically thought to indicate clinically relevant anxiety (Womble et al., 2021). The internal consistencies for Study 3 were: .953 for STAI-1, and .910 for STAI-2. For Study 4 they were .953 for STAI-1, and .922 for STAI-2.

Behavioural tasks

Study 4 is the only study which included behavioural tasks. In the study, three executive function tasks were selected to investigate whether task performance differs according to the mental health profiles of our neurotypical participants and/or vary as a function of their mental health symptoms. These three tasks were selected as they are frequently employed in the field, especially in psychological experiments that seek to demonstrate cognitive-behavioural differences associated with anxious and depressive symptoms (Peschard et al., 2013; Segal et al., 2015). It was decided that use of emotional stimuli should be avoided as there is already an

extensive body of literature demonstrating the effects of anxious and depressive symptoms in such tasks (E. S. Becker et al., 2001; Suárez-Pellicioni et al., 2015).

Several exclusion criteria were applied across all three tasks. Any trials with reaction time of less than 100 ms were removed as these were likely accidental key-presses or responses where participants were not engaging with the task (Luce, 1991). An upper limit on reaction time was not set, to avoid potentially eliminating trials that took long as a result of any effects of various mental health symptoms. As a result, median reaction times were used for analyses. Participants were included if they passed task-specific attention checks, which i) were nested throughout the task and ii) was given as a questionnaire at the end of the study. Participants were removed if they scored below 80% for attention checks nested in the task, and if they answered incorrectly to the attention check questionnaire item specific to the task.

Stroop Stroop is a widely used paradigm that measures inhibition and attention (Stroop, 1935), including in clinical conditions such as anxiety and depression (E. S. Becker et al., 2001; Nuño et al., 2021). In its simplest version, which was used in this study, participants are presented with a colour word and are required to indicate whether the name of the colour and the font colour are the same or different. Studies have found generally higher accuracy and faster reaction time in congruent trials (e.g., the word *blue* shown in blue) than in incongruent trials (e.g., the word *blue* shown in red; MacLeod, 1991). The task consisted of 6 blocks of 24 Stroop trials (12 trials each of congruent and incongruent trials) and 2 attention check trials (a total of 144 Stroop trials and 12 attention check trials). Participants took self-timed breaks between blocks. Accuracy and reaction time were collected for congruent and incongruent trials separately. To quantify the Stroop effect, the difference between incongruent and congruent trials was calculated for accuracy and reaction time, which was used for data analysis. Attention checks nested in the task asked participants to press space when they saw a screen with the words "Attention Check." In the attention check questionnaire at the end of the study, participants were asked if they had to match the word to the shape, colour, or size of the letters. Two participants who did not meet the behavioural exclusion criteria were removed prior to analysis. Moreover, one participant whose accuracy score was more than 12 standard deviations away from the mean (congruent

trials: 13.89%, incongruent trials: 11.11%) was removed. This participant was removed from analysis for all tasks, as it was uncertain whether they completed the tasks having understood the instructions properly. For Study 4 analyses, therefore, the initial sample size became 222 (rather than 223) after removing this clear outlier. After applying the behavioural exclusion criteria, the number of participants analysed for the Stroop task was 220.

N-back N-back is a task designed to measure working memory (W. K. Kirchner, 1958). In this study, a 2-back task was used, where participants were shown a series of letters and were instructed to indicate whether the letter shown on the screen, which remained for 2 seconds, was the same or different as the letter shown two trials prior. The task consisted of 5 blocks of 30 trials and 1 attention check trial (a total of 150 n-back trials and 5 attention check trials). Accuracy and reaction time were collected. For data analysis, trials where participants did not produce a response were removed as it was not possible to determine whether it was due to lack of attention or their inability to give a response in the given time window (2 seconds). Attention checks nested in the task asked participants to press space when they saw a screen with the words "Attention Check," which were presented before the break between blocks. In the attention check questionnaire at the end of the study, participants were asked if they had to match the letter that was one, two, or three letters before the one they were seeing. After applying the behavioural exclusion criteria, the number of participants analysed for the n-back task was 193.

Matrix reasoning Wechsler Abbreviated Scale of Intelligence (Second Edition, WASI-II) is a widely used test of cognitive abilities, composed of four sub-tests (Wechsler, 2011). The matrix reasoning (MR) sub-test was used for this study to test nonverbal abstract problem solving. In the task, a series of visual puzzles with one missing part were displayed, and participants were asked to select one of the five options that fit the missing part best. The task consisted of 2 practice trials and 30 main trials, which increased in difficulty on every trial. The task ended automatically once three consecutive incorrect responses were recorded. The number of correct responses was transformed into T scores based on age using the WASI-II conversion tables. No

participants were excluded, resulting in the analysis sample of 222 for the MR task.

2.2.3 Statistical Analyses

All statistical analyses were performed using R (R Core Team, 2022) and RStudio (version 2022.12.0+353; RStudio Team, 2022), with an alpha threshold of $p < .05$ (two-tailed).

Chi-squared tests

To ease the comparisons between studies that used different measures, participants were categorised using cut-offs from each questionnaire (e.g., mild, moderate, severe). Chi-squared tests were then used to statistically compare the proportions of participants falling into the different categories on each mental health measure between studies. Participant proportions in Study 1 (the secondary, national data sets) were treated as references, which were then compared against participant proportions on the corresponding mental health measures in Studies 2 and 3 (the primary data sets). Given that the large sample sizes in Study 1 would render most group comparisons statistically significant, the effect size (Cramer's V) was interpreted, which ranges from 0 to 1 (Cohen, 1988).

Latent profile analysis

Next, to identify any distinct mental health profiles among participants in a multivariate manner, an LPA was conducted across participants in Studies 3 and 4. A combined sample was deemed more advantageous than clustering separate study samples as this would provide a larger and more representative sample to identify a variety of mental health symptom sub-groups, thereby ensuring reasonable sub-group sizes for subsequent group comparisons. LPA was performed using the mclust package (Scrucca et al., 2016). Bayesian information criterion (BIC) and integrated complete-data likelihood (ICL) were used to determine the best-fitting model. Items included in the LPA were the total questionnaire scores of the BDI-II, STAI-1, STAI-2, PHQ-8, and WEMWBS, and the sub-scale total scores of anxiety, depression, and stress on the DASS-21.

Questionnaire scores were not normally distributed, as determined by the Shapiro-Wilk normality test. Kruskal-Wallis test was employed to compare the score means between latent profiles, followed by Dunn's test for pair-wise comparisons.

Trend analysis

Finally, trend analyses were conducted to assess whether there is a trend in behavioural task performance outcomes (i.e., accuracy, median reaction time, and reaction time variability for Stroop and n-back, and T-scores for MR) between latent profiles. Specifically, orthogonal polynomial coding was used to see if there are polynomial effects on the outcome variables according to symptom severity. A contrast matrix was generated according to the number of latent profiles (i.e., $n - 1$). As behavioural task performance outcomes were not normally distributed, Kruskal-Wallis test and Dunn's test were used to determine whether the latent profile had an effect on behavioural task performance outcomes.

2.3 Results

2.3.1 Descriptive Statistics

Table 2.3 summarises the demographic information of each data set used in this study. Median age groups are shown instead of median age as the secondary data sets did not report specific age for participants.

Table 2.3: Descriptive statistics for demographic information. Mean age groups are reported, rather than exact age, as primary data sets do not provide exact ages of each responders. For Studies 3 and 4, participants were asked to identify their gender from three options: male, female, other.

Data set	Questionnaire	Male (%)	Female (%)	Other (%)	Median Age Group
EQoLS	WHO-5	44.3	55.7		40 to 44
EHIS	PHQ-8	43.9	56.1		45 to 49
HSE 2016	GHQ-12	43.0	57.0		40 to 44
	WEMWBS	43.0	57.0		40 to 44
HSE 2018	GHQ-12	44.6	55.4		40 to 44
HSE 2019	WEMWBS	43.8	56.2		40 to 44
Study 2	WEMWBS-7	23.0	75.9	1.10	50 to 54
Study 3	All	24.3	75.1	0.60	25 to 29
Study 4	BDI-II, STAI-1, STAI-2, DASS-21, PHQ-8, WEMWBS	33.2	65.9	0.90	25 to 29

2.3.2 Comparisons of the Prevalence of Mental Health Traits

Figure 2.1 shows the proportions of participants classified into different mental health categories based on their questionnaire scores in Studies 1-3.

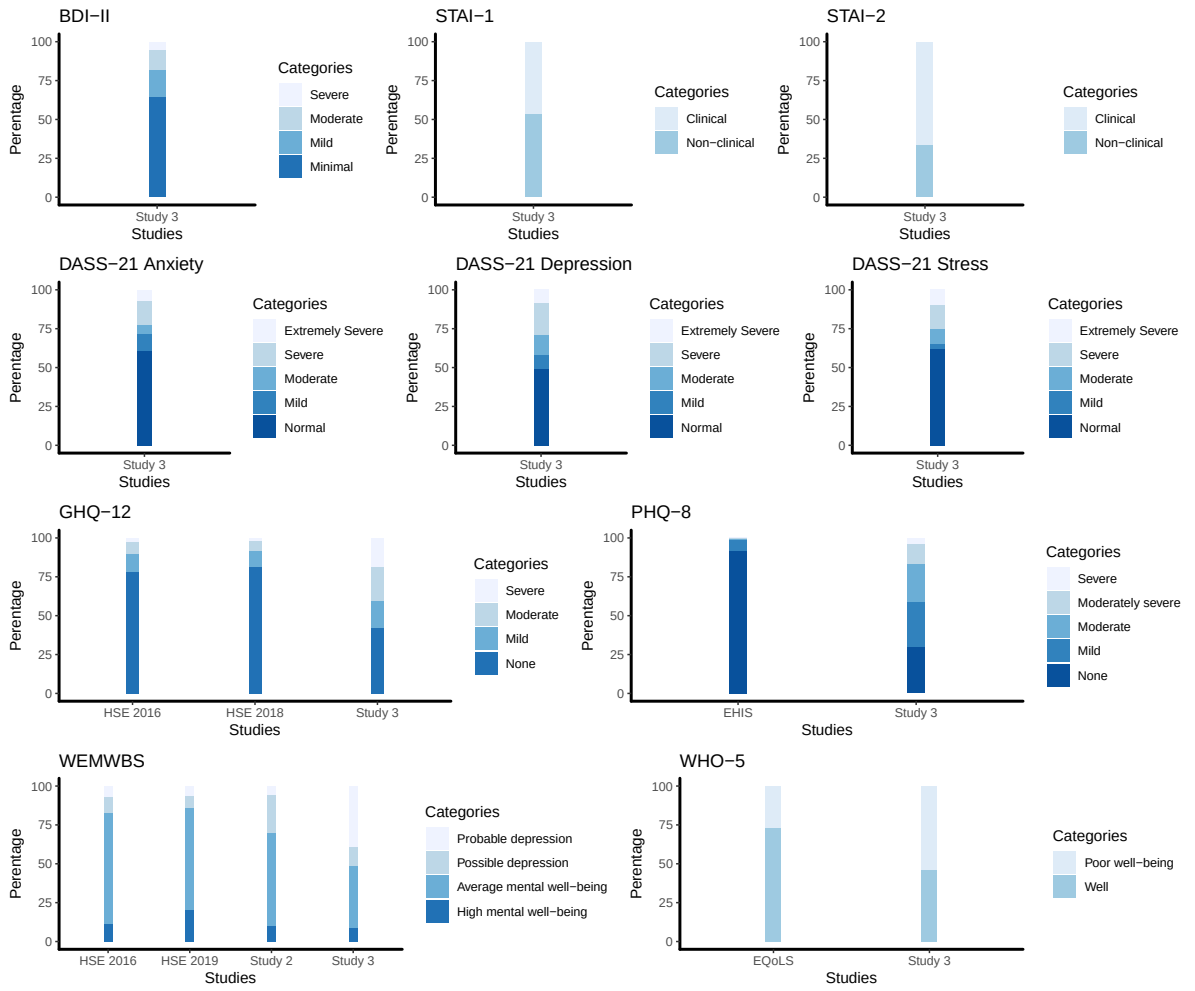


Figure 2.1: Questionnaire categories for Studies 1-3. Proportions of questionnaire categories per questionnaire, compared across studies are shown. Study 1 data (HSE 2016, 2019, EHIS, and EQoLS) are from secondary data sets, Study 2 and 3 are from primary data sets obtained from typical volunteers for psychology studies.

Figure 2.2 shows confidence intervals for comparisons of questionnaire measures. For ease of reference, Study 1 included the national surveys EQoLS, EHIS, HSE (2016, 2018, 2019), while Studies 2 and 3 included primary data collection from typical volunteers for psychological experiments. Data are organised by measure, and compared across studies that include that measure. Chi-squared test was done only for questionnaire measures that were available in any of the Study 1 data sets. It therefore excludes BDI-2, STAI-1, STAI-2, and all sub-scales of DASS-21.

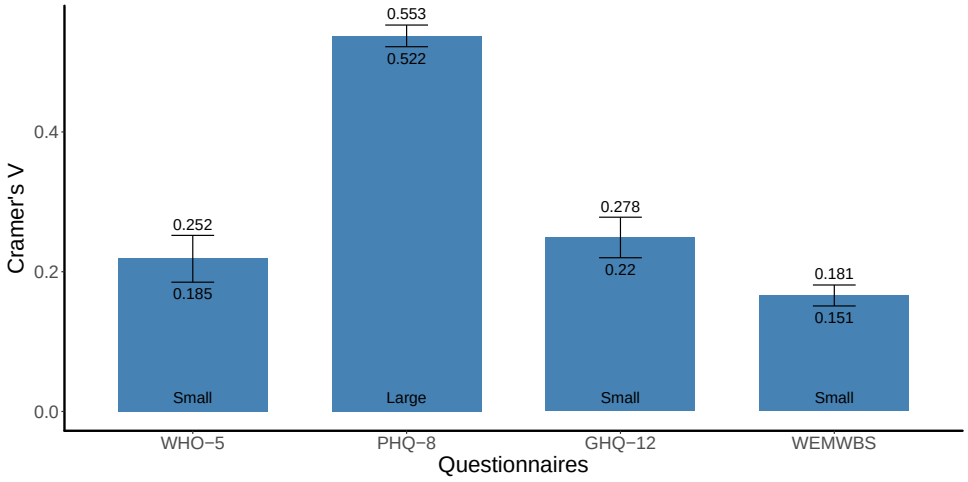


Figure 2.2: Cramer's V for chi-squared test comparisons for questionnaires between Studies 1-3. Chi-squared test comparisons of proportion of questionnaire categories were as follows: WHO-5: between EQoLS and Study 3, PHQ-8: between EHIS and Study 3, GHQ-12: between HSE 2016 and 2018, and Study 3, and WEMWBS: between HSE 2016 and 2019, Studies 2 and 3. Error bars show the 95% confidence intervals. The effect sizes are written in the bottom of each bar.

For the WHO-5, median scores were 17 for Study 1 (EQoLS, range: 0-25), and 13 for Study 3 (range: 0-25). There were significant differences in the proportions of WHO-5 categories between the two studies [$\chi^2(1) = 145.45$, $p < .001$], with a small effect size [Cramer's V = .219, df = 1, 95% CI: .185, .252]. 73.2% of participants were categorised as "being well" in EQoLS, compared to 45.7% in Study 3. The rest were categorised into "well" (EQoLS: 26.8%, Study 3: 54.3%).

For the PHQ-8, median scores were 0 for Study 1 (EHIS, range: 0-24) and 8 for Study 3 (range: 0-24). There were significant differences in the proportions of PHQ-8 categories between the two studies [$\chi^2(4) = 2440.3$, $p < .001$], with a large effect size [Cramer's V = .538, df = 1, 95% CI: .522, .553]. 98.5% of EHIS participants had "none" (91.5%) or "mild" (7.0%) depression, compared to 58.7% of Study 3 participants ("none": 29.6%, "mild": 29.1%). The rest were categorised into "moderate", "moderately severe", and "severe" depression categories (EHIS: 1.5%, Study 3: 41.3%).

For the GHQ-12, median scores were 10 for Study 1 (HSE-2016 and HSE-2018, range: 0-36 for both data sets), and 14 for Study 3 (range: 0-36). There were significant differences in the proportions of GHQ-12 categories among studies [$\chi^2(6) = 498.73$, $p < .001$], with a small effect size [Cramer's V = .249, df = 1, 95% CI: .220, .278]. While 89.9% of HSE-2016 participants

and 92.0% of HSE-2018 participants had "none" or "mild" risks of mental health conditions, only 59.7% of Study 3 participants were categorised as such. The rest were categorised into "moderate" or "severe" categories (HSE-2016: 10.1%, HSE-2018: 8.0%, Study 3: 40.3%). Significant differences remained in pair-wise chi-squared test comparisons involving Study 3, with Cramer's V being .379 [df = 1, 95% CI: .344, .414] for HSE-2016 and Study 3 comparison, and Cramer's V being .416 [df = 1, 95% CI: .381, .450] for HSE-2018 and Study 3 comparison, both indicative of a medium effect size. There was no significant difference between HSE-2016 and HSE-2018 [Cramer's V = .047, df = 1, 95% CI: .014, .08].

For the WEMWBS, median scores were 52 for Study 1 (HSE-2016, range: 18-70), 53 for another data set from Study 1 (HSE-2019, range: 14-70), and 44 for Study 3 (range: 14-70). For the WEMWBS-7, the transformed median score was 22.4 (range: 7-35) for Study 2. There were significant differences in the proportions of WEMWBS categories between studies [$\chi^2(9) = 1319.5$, $p < .001$], with a small effect size [Cramer's V = .166, df = 3, 95% CI: .151, .181]. 82.7% of HSE-2016 participants, 86.2% of HSE-2019 participants, 70.2% of Study 2 participants, and 48.6% of Study 3 participants had "average mental well-being" or "high mental well-being". The rest were categorised into possible and probable depression (HSE-2016: 17.4%, HSE-2019: 13.8%, Study 2: 29.7%, Study 3: 51.4%). Significant difference remained in pairwise comparisons between studies, with Cramer's V [df = 1] ranging from .113 (small effect size) to .416 (medium effect size).

Further details on questionnaire category comparisons can be found in Section A.1.1.

2.3.3 Latent Profile Analysis

An LPA was conducted on the Studies 3 and 4 participants ($N = 717$) to classify participants based on various mental health symptoms collected from the self-report questionnaires. Five cluster profiles with ellipsoidal, equal shapes (VEE from mclust) was the best fit model (BIC = -36376.49, ICL = -36641.02).

Figure 2.3 shows the five-cluster solution. The "no mood symptoms" profile has the lowest mental health symptoms and was the smallest group ($n = 37$, 5.16%). The second group

is the "low mood symptoms" profile (n = 153, 21.34%), which has higher scores across all questionnaires when compared to the "no mood symptoms" profile but would still be categorised as mostly having minimal mood symptoms according to median questionnaires scores. The third group is the "mild mood symptoms" profile (n = 170, 23.71%), whose median questionnaire scores fell in the minimal to moderate range across all questionnaire categories. The fourth group is the "moderate mood symptoms" profile (n = 259, 36.12%), whose median scores were in the mild to severe range across all questionnaire categories. The fifth and final group is the "significant mood symptoms" profile (n = 98, 13.67%), whose median questionnaire scores were in mild to extremely severe range across all questionnaire categories.

Descriptive summaries of questionnaire scores for each latent profile can be found in Table 2.4. There were significant differences in mean questionnaire scores, with a large effect size across all questionnaires ($.486 \leq \eta^2 \leq .658$). Dunn's multiple comparisons revealed significant differences between latent profiles across all questionnaires ($.001 < p < .05$) except for between "no mood symptoms" and "low mood symptom" profiles for STAI-2, DASS-21 anxiety and depression, and PHQ-8, and between "significant mood symptom" and "moderate mood symptom" profiles for WEMWBS.

Distribution of questionnaire scores per latent profile can be found in Section A.1.1

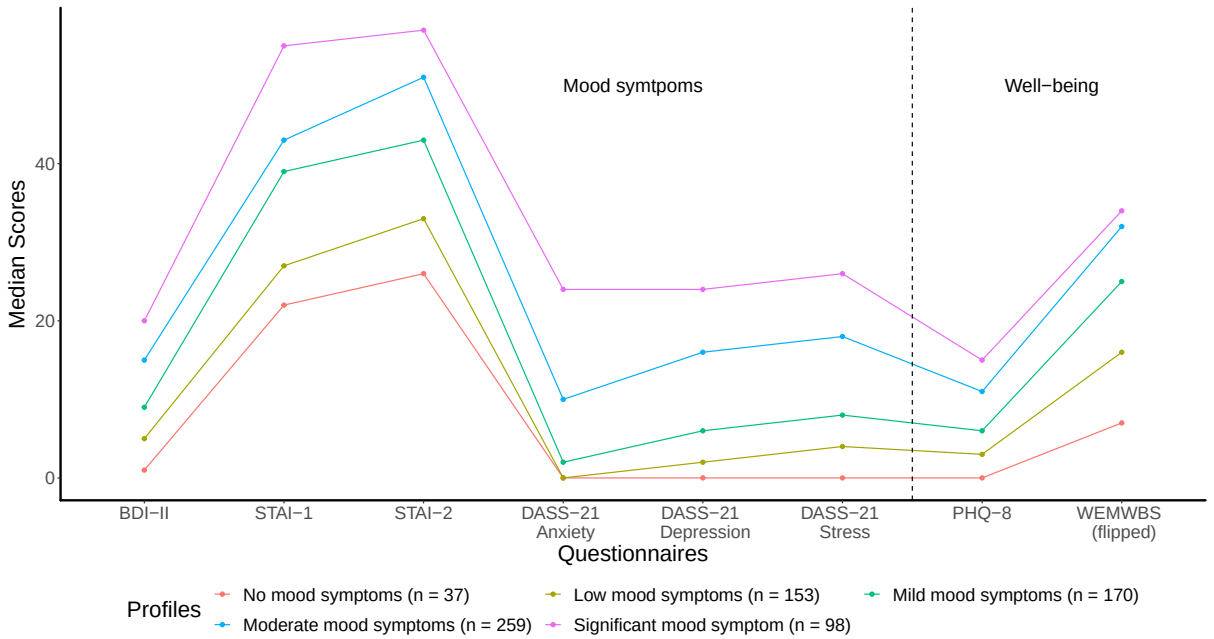


Figure 2.3: Latent profiles consisting of Studies 3 and 4 participants ($N = 717$). Total scores of the BDI-II, STAI-1, STAI-2, sub-scales of anxiety, depression, and stress from DASS-21, PHQ-8, and WEMWBS were used to create latent profiles. WEMWBS scores are flipped as, unlike the other questionnaires, higher scores mean less symptom severity. Flipped scores were calculated by subtracting the scores from highest score possible on WEMWBS, which is 70. Minimum scores for STAI-1 and STAI-2 are 20, while they are 0 for all other questionnaires.

Table 2.4: Descriptive statistics of latent profiles consisting of Studies 3 and 4 participants (N = 717). Median, minimum, and maximum scores per questionnaire are shown for each latent profile. The last three columns represent adjusted Dunn's multiple comparisons. * $p < .05$, ** $p < .01$, *** $p < .001$.

Profile	Median	Min	Max	No mood symptoms	Low mood symptoms	Mild mood symptoms	Moderate mood symptoms
BDI-II				$\chi^2(4) = 390.06$***, $\eta^2 = .542$			
No mood symptoms	1	0	4	-			
Low mood symptoms	5	0	15	3.14*	-		
Mild mood symptoms	9	0	19	6.44***	5.32***	-	
Moderate mood symptoms	15	1	49	11.57***	14.30***	8.76***	-
Significant mood symptoms	11	0	49	12.59***	14.33***	9.94***	3.34**
STAI-1				$\chi^2(4) = 350.27$***, $\eta^2 = .486$			
No mood symptoms	22	20	25	-			
Low mood symptoms	27	20	40	3.14*	-		
Mild mood symptoms	39	21	57	8.69***	8.98***	-	
Moderate mood symptoms	43	20	71	10.85***	13.05***	3.34**	-
Significant mood symptoms	55	22	80	12.82***	14.68***	7.08***	4.79***
STAI-2				$\chi^2(4) = 462.13$***, $\eta^2 = .643$			
No mood symptoms	26	23	30	-			
Low mood symptoms	33	23	41	2.52	-		
Mild mood symptoms	43	28	57	8.14***	9.11***	-	
Moderate mood symptoms	51	25	69	12.07***	16.27***	6.52***	-
Significant mood symptoms	57	37	77	13.45***	16.49***	8.82***	4.00***
DASS-21 Anxiety				$\chi^2(4) = 472.24$***, $\eta^2 = .658$			
No mood symptoms	0	0	2	-			
Low mood symptoms	0	0	10	1.65	-		
Mild mood symptoms	2	0	10	3.48**	2.95*	-	
Moderate mood symptoms	10	0	20	8.99***	12.53***	9.62***	-
Significant mood symptoms	24	16	42	13.72***	18.12***	15.90***	9.00***
DASS-21 Depression				$\chi^2(4) = 435.16$***, $\eta^2 = .606$			
No mood symptoms	0	0	6	-			
Low mood symptoms	2	0	14	2.43	-		
Mild mood symptoms	6	0	18	5.44***	4.86***	-	
Moderate mood symptoms	16	0	42	11.01***	14.61***	9.60***	-
Significant mood symptoms	24	2	42	13.01***	15.96***	12.01***	4.85***
DASS-21 Stress				$\chi^2(4) = 412.64$***, $\eta^2 = .574$			
No mood symptoms	0	0	2	-			
Low mood symptoms	4	0	16	3.52**	-		
Mild mood symptoms	186	0	22	5.98***	3.95***	-	
Moderate mood symptoms	18	0	42	11.23***	13.03***	9.00***	-
Significant mood symptoms	26	6	42	13.76***	15.54***	12.38***	5.75***
PHQ-8				$\chi^2(4) = 469.08$***, $\eta^2 = .653$			
No mood symptoms	0	0	3	-			
Low mood symptoms	3	0	9	2.77	-		
Mild mood symptoms	6	0	12	6.27***	5.66***	-	
Moderate mood symptoms	11	1	23	11.96***	15.65***	9.78***	-
Significant mood symptoms	15	2	24	13.47***	16.18***	11.53***	4.19***
WEMWBS				$\chi^2(4) = 371.59$***, $\eta^2 = .516$			
No mood symptoms	63	58	70	-			
Low mood symptoms	54	24	70	-3.34***	-		
Mild mood symptoms	45	28	66	-8.26***	-7.96***	-	
Moderate mood symptoms	38	14	68	-12.07***	-14.79***	-6.29***	-
Significant mood symptoms	36	14	60	12.21***	-13.48***	-6.76***	-1.99

2.3.4 Comparisons of Behavioural Task Performance

Simple correlations

Simple correlations of all self-report measures and behavioural variables can be found in Table 2.5. As expected, all the self-report questionnaire scores were highly correlated with one another ($.001 \leq p \leq .05$). Some of the behavioural task performance correlated with age and anxious traits. Significantly correlated variables were as follows: i) Stroop task accuracy difference with state and trait anxiety (STAI-1 and STAI-2) and anxiety sub-scale of DASS-21, ii) Stroop median reaction time for congruent trials with age, iii) Stroop median reaction time for incongruent trials with age, trait anxiety (STAI-2) and anxiety sub-scale of DASS-21, iv) Stroop median reaction time difference with state anxiety (STAI-1), and v) n-back median reaction time with trait anxiety (STAI-2).

Table 2.5: Simple correlations between self-report measures and behavioural task performance. With the exception of WEMWBS, higher scores on the questionnaires indicate more severe symptoms. BDI-2: depressive traits, STAI-1: state anxiety, STAI-2: trait anxiety, DASS-21 anx: anxious traits, DASS-21 dep: depressive traits, DASS-21 str: stress traits, PHQ-8: depressive traits, WEMWBS: mental well-being, whereby higher scores indicate better mental well-being, and lower scores indicate potential depression. Acc: accuracy, rt: median reaction time, rt (sd): reaction time standard deviation. STR: Stroop, MR: T-score calculated from the MR sub-scale of the WASI-II. All measures were log transformed and centred prior to analysis. * $p < .05$, ** $p < .01$, *** $p < .001$.

					DASS-21					Stroop									N-back		
	Age	BDI-2	STAI-1	STAI-2	anx	dep	str	PHQ-8	WEMWBS	acc con	acc incon	acc diff	rt con	rt incon	rt diff	rt (sd) con	rt (sd) incon	rt (sd) diff	acc	rt	rt (sd)
Age																					
BDI-2	-.640**																				
STAI-1	-.729***	.931***																			
STAI-2	-.691***	.978***	.967***																		
DASS-21 anx	-.747***	.934***	.930***	.951***																	
DASS-21 dep	-.610**	.986***	.936***	.975***	.931***																
DASS-21 str	-.693***	.967***	.949***	.973***	.960***	.962***															
PHQ-8	-.689***	.987***	.944***	.982***	.945***	.976***	.970***														
WEMWBS	.514*	-.967***	-.919***	-.960***	-.879***	-.974***	-.933***	-.957***													
STR acc con	.242	-.299	-.382	-.361	-.392	-.342	-.353	-.363	.344												
STR acc incon	.211	-.366	-.405	-.392	-.419	-.405	-.405	-.409	.382	.916***											
STR acc diff	-.373	.348	.423*	.439*	.454*	.376	.393	.413	-.391	-.851***	-.637**										
STR rt con	.588**	-.343	-.358	-.384	-.402	-.313	-.344	-.355	.252	.003	-.047	-.330									
STR rt incon	.629**	-.376	-.408	-.428*	-.447*	-.345	-.382	-.398	.284	.070	.003	-.405	.979***								
STR rt diff	.384	-.356	-.436*	-.415	-.410	-.340	-.374	-.399	.337	.331	.228	-.515*	.352	.528*							
STR rt (sd) con	.206	-.061	-.063	-.094	-.089	-.037	-.034	-.058	.026	-.283	-.350	-.077	.837***	.780***	.150						
STR rt (sd) incon	.232	-.022	-.020	-.056	-.070	.014	.002	-.021	-.054	-.240	-.302	-.104	.833***	.786***	.138	.930***					
STR rt (sd) diff	-.016	.149	.161	.128	.098	.184	.164	.135	-.233	-.135	-.137	.002	.390	.365	-.037	.519*	.748***				
N-back acc	-.240	.141	.073	.139	.097	.103	.098	.115	-.084	.407	.447*	-.059	-.591**	-.591**	-.220	-.596**	-.620**	-.377			
N-back rt	.291	-.401	-.374	-.433*	-.389	-.403	-.396	-.367	.373	.091	.095	-.347	.720***	.711***	.313	.547**	.529*	.188	-.527*		
N-back rt (sd)	.044	-.218	-.146	-.232	-.153	-.215	-.196	-.159	.200	-.265	-.266	-.052	.544**	.537**	.232	.544**	.533*	.245	-.726***	.833***	
MR	-.235	.037	.057	.017	-.037	.000	-.008	.023	-.002	.484*	.466*	-.326	-.462*	-.448*	-.105	-.510*	-.475*	-.247	.641**	-.287	-.419

Trend analysis

Orthogonal polynomial coding was used to test for any trends in behavioural task performance between the five profiles, resulting in three contrast matrices: linear, quadratic, cubic, and quartic. This type of analysis was deemed appropriate as there is a clear hierarchical relationship between the profiles (mood symptoms increase from "no", "low", "mild", "moderate", to "significant mood symptom" profiles). Trend analysis was conducted on accuracy, median reaction time, and reaction time variability for Stroop and n-back, and T-scores for MR. Only significant trends are reported below, and a statistical summary for all variables (including non-significant trends) can be found in Section A.1.1. Significant trends are illustrated in Figure 2.4.

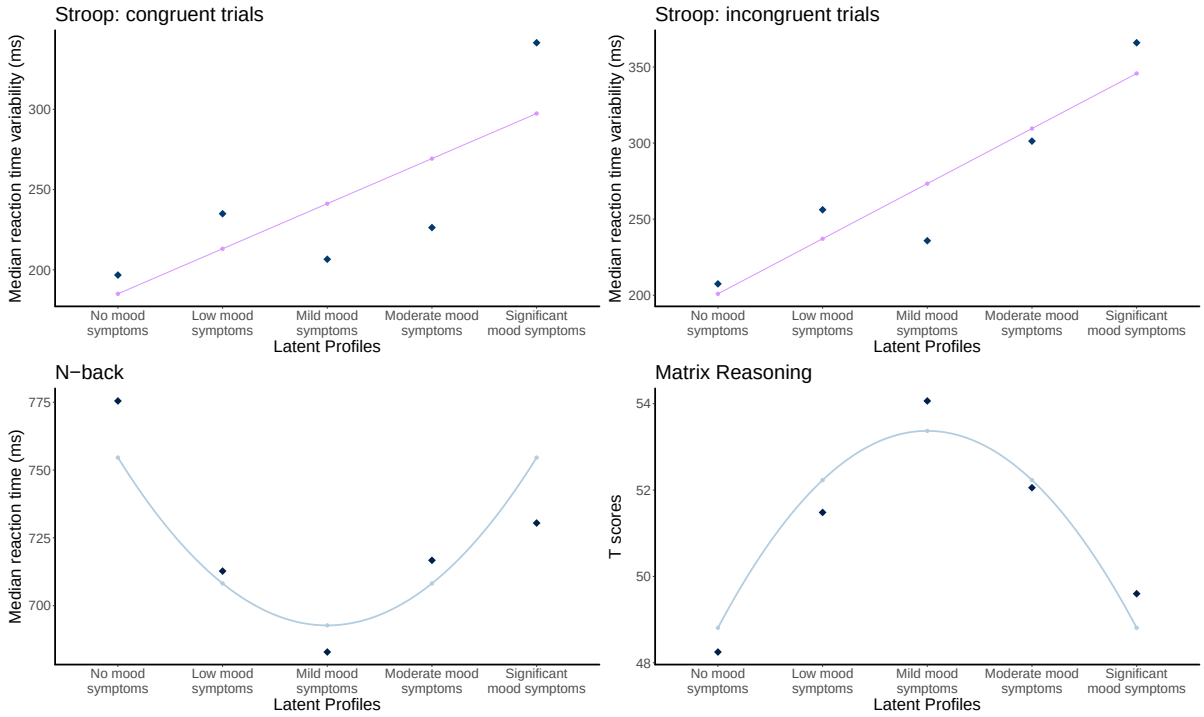


Figure 2.4: Relationships between latent profiles and behavioural task performance. Dark diamond data points indicate actual mean values, and small dots indicate predicted values based on the best fitting polynomial contrast matrix from the trend analysis. Top: Stroop tasks, linear trend for reaction time variability for (left) congruent trials and (right) incongruent trials. Bottom: (left) quadratic trend for median reaction time for n-back task, (right) quadratic trend for MR T-scores.

For the Stroop task, linear trend was the best fitting model for reaction time variability for both congruent trials [estimate = 88.77, p = .013, adjusted R^2 = .039], and incongruent trials [estimate = 114.52, p = .033, adjusted R^2 = .012]. However, no main effect of latent profile on reaction time variability was found on either congruent [$\chi^2(4)$ = 2.23, p = .694, η^2 = -.008] or

incongruent trials [$\chi^2(4) = 3.62$, $p = .460$, $\eta^2 = -.002$].

For the n-back task, median reaction time was shown to have a quadratic trend [estimate = 57.87, $p = .026$, adjusted $R^2 = .011$]. Again, no significant main effect of latent profile was found [$\chi^2(4) = 5.75$, $p = .218$, $\eta^2 = .009$].

For the MR, T-scores were shown to have a quadratic trend [estimate = -4.27, $p = .008$, adjusted $R^2 = .020$]. Similar to the Stroop and n-back, there was no significant main effect of latent profile [$\chi^2(4) = 6.92$, $p = .140$, $\eta^2 = .013$].

2.4 Discussion

The present study investigated the prevalence and effects of sub-clinical levels of mental health symptoms in what would typically be considered as samples of neurotypical participants in psychology experiments. Across several studies, comparisons between samples of volunteers for psychological studies and national data sets revealed a greater proportion of mental health symptoms in samples of psychology volunteers. Small to large effect sizes were found across all comparisons. These results indicate that individuals who volunteer to take part in psychological studies are more likely to have higher symptom levels of various mental health conditions compared to the general population.

Next, LPA was conducted to investigate any multi-dimensional clustering of our participants. A five-cluster solution was found to be best, whereby the participants were divided into “no”, “low”, “mild”, “moderate”, and “significant mood symptoms” profiles. Results showed that the smallest group was the “no mood symptoms” profile (5.16%), and the majority of the participants fell into “low”, “mild” or “moderate mood symptoms” profiles (81.17%). However, a significant proportion of participants were clustered into the “significant mood symptoms” profile (13.67%). In addition to highlighting once again that samples of “neurotypical” volunteers for psychology studies are not without mood symptoms, these data show the presence of five sub-groups in what is typically considered to be a homogeneous sample of “healthy volunteers”.

To conclude, polynomial trend analysis was used to determine whether the profiles identified through LPA affected performance on standard tests of executive function and intelligence,

the Stroop and n-back tasks, and the MR sub-test of the WASI-II. Simple correlations revealed significant relationships between some of Stroop task performance (accuracy difference between congruent and incongruent trials, median reaction time for incongruent trials, and median reaction time difference between congruent and incongruent trials) and anxious traits, as well as median reaction time for n-back and anxious traits.

Trend analysis revealed significant linear trends for Stroop task for reaction time variability for congruent and incongruent trials. The "no mood symptoms" profile had the smallest reaction time variability for both congruent and incongruent trials. However, the "no mood symptoms" group had the longest median reaction time for n-back, and also performed the worst in MR, which both showed a quadratic trend, such that the "mild mood symptoms" group performed the best in both n-back and MR. Despite this quadratic relationship, when using questionnaire categories, there would be no distinction between "no mood" and "low mood symptoms" profiles. This is because the two profiles had similar range of scores that would be grouped into the same symptom severity categories (i.e., none or minimal depression or anxiety symptoms). This suggests that even what seems to be subtle differences in questionnaire scores can influence the behavioural task outcomes, and that using questionnaire scores rather than pre-defined questionnaire categories may be better practice, as was done in the present study.

It should be noted that the "no mood symptoms" profile was the smallest group. The proportion of "no mood symptoms" profile was 5.16% for Studies 3 and 4 combined, and 7.17% just for Study 4. These proportions are similar to those found in previous studies (Crawford et al., 2011; Whisman & Richardson, 2015), when each questionnaire is considered on its own. The proportion of study participants who would score 0 (20 for STAI, as that is the lowest possible score) across all questionnaires (BDI-II, STAI-1, STAI-2, DASS-21, PHQ-8), therefore, is unknown. It is perhaps possible that there are sub-groups even within the "no mood symptoms" profile, possibly comprised of those who i) truly do not have mood symptoms, and ii) are not aware of their mood symptoms, driven by factors such as dissociation (Lyssenko et al., 2018) or alexithymia (Nemiah, 1977). Self-report questionnaires rely on participants having awareness and being sensitive to their emotions and internal bodily states. It is possible, therefore, that a person could score 0 on a self-report questionnaire if they have limited awareness or sensitivity

to their internal states despite having, for example, high depressive symptoms, rather than having no mood symptoms. Further work is needed to investigate whether scoring 0 on questionnaires indicates a lack of mood symptoms, or a lack of awareness of the presence of mood symptoms. This dissociation could have further implications for the utility of self-report questionnaires on mental health symptoms and on the meaning of given responses.

The current study provides empirical evidence that standard participant pools have more mental health symptoms than the general population. However, it should be noted that even in the national data sets, at least 50% of participants were not included in the analysis as they did not meet the inclusion criteria as "neurotypical". This may suggest that people who have no psychiatric diagnoses and do not take any psychotropic medications are not representative of the trend in the general population. However, it is essential that sub-clinical and clinical levels of mental health symptoms are controlled for when investigating human cognition and behaviour, as Study 4 highlights the significant effects even minimal sub-clinical levels of mental health traits can have on performance in very standard, purely cognitive tasks.

One thing to note is the somewhat discordant results between the simple correlation results and the trend analysis. This may point to the fact that having more of a comprehensive picture of a person's mental health traits, such as by using latent profiles, rather than using single-test questionnaire scores, provides a better sense of the effects of mental health traits on cognitive tasks. There may be wider implications not only in studies using emotional stimuli (Segal et al., 2015; Thoresen et al., 2016), but also in complex behavioural paradigms, where clinical levels of mental health symptoms have been shown to influence task performance (Ashwin et al., 2012; Yoon et al., 2014). However, it should be recognised that creating latent profiles requires a large sample size, and there are practical limitations to doing this, especially when conducting in-person experiments with clinical participants.

One of the limitations of the present study is that questionnaires used to create the latent profiles assessed mostly depressive (BDI-II, DASS-21 depression, PHQ-8, and WEMWBS) and anxious symptoms (STAI-1, STAI-2, DASS-21 anxiety). It is therefore possible that our latent profiles are constructed based on one's depressive and anxiety symptoms, rather than a comprehensive mental health profile. However, these questionnaires were chosen as depression

and anxiety are common mental health conditions. Future studies should therefore use more varied types of questionnaires that quantify other common mental health-related traits, such as loneliness. As many of the questionnaires used in creating the latent profiles looked at depression and anxiety, it would be interesting to look at the factor structure of the questionnaire items combined together (depression and anxiety separately) and investigate whether it results in different clustering results.

Another limitation of the study, and an aspect that can be generalised to many psychology studies, is the age of our participants. Compared to national data sets (median age group: 40-44), participants in Studies 3 and 4 were significantly younger (median age group: 25 to 29). Although Study 2 was an online psychology experiment, due to its large scale (N = 43,094), it had more representative sampling of participants (median age group: 50 to 54), as in national data sets. Age is an important factor to consider in psychology experiments as it correlates with standard cognitive task performance, including Stroop (as shown by significant correlations in the present study; Chen & Hsieh, 2023; Ghisletta et al., 2018; Mazurek et al., 2015). Furthermore, increased intra-individual variability, such as a person's response variability within a single testing session, is greater among older adults, especially in choice reaction time tasks, of which the Stroop and n-back are examples (Dykiert et al., 2012). While age is a factor to consider in cognitive differences, that may not be the case for mental health traits. The latest Quality of Life in the UK report (October to December 2022) on personal well-being by the Office for National Statistics showed no age differences in anxiety and mental well-being (Office for National Statistics, 2023). However, again, this finding is from a national data set, and there may be an effect of age in mental health traits in a typical psychology experiment population pool. Further investigations are required to assess if there are differences in mental health traits according to various age groups in those who take part in psychology studies.

The current study provides insights into the prevalence and effects of sub-clinical levels of mental health symptoms. The ongoing reproducibility crisis observed in psychology might be partially explained by the lack of accounting for sub-clinical levels of mental health symptoms in our participants, and the lack of consideration for diversity within the neurotypical population. This series of studies shows that having measures of mental health symptoms might be crucial

in finding the true effects of behavioural tasks in psychology research.

Chapter 3

Effects of conditioning on pain perception

Abstract

Pain experience can be altered by the expectations of the upcoming pain stimulus, producing well-known phenomena such as placebo effects. Such effects are explained by Bayesian theories of perception, which suggest expectations about sensory stimuli are combined with sensory evidence according to their precision to generate a percept. It has been suggested that Bayesian inference is atypical in autism, driven by highly precise bottom-up sensory evidence rather than top-down expectations. In addition, recent research indicates that interoceptive difficulties in autism (a reduced ability to identify and perceive bodily sensations) are better explained by co-occurring alexithymia. This latter finding suggests that any atypical inference in autism, at least within the interoceptive domain, may be a product of co-occurring alexithymia. The present study used a placebo hypoalgesia paradigm to test Bayesian accounts of autism and alexithymia. The placebo hypoalgesia task permits manipulation of expectations (the magnitude of pain relief) as well as an assessment of individual differences in the perception of stimuli (perceived pain level), allowing testing of Bayesian inference. The present study investigated whether the differences observed in the initial placebo effect calculated by pain intensity ratings and anticipatory galvanic skin response (aGSR), and the extinction function could be explained by individual differences in autistic and alexithymic traits. Results showed it is alexithymic traits, not autistic traits, that predict the magnitude of the initial placebo effect measured by

pain intensity ratings and the extinction function. This study provides further evidence for the alexithymia hypothesis.

3.1 Introduction

Pain experience can be influenced by prior expectations about that said pain (McGrath, 1994). Altering the expectation of upcoming pain is sufficient to create an enduring change in perception, generating well-established phenomena such as nocebo and placebo effects (Colloca & Benedetti, 2006; Colagiuri et al., 2015).

Placebo hypoalgesia (Figure 3.1) is driven by pain relief expectations (Au Yeung et al., 2014), generated via verbal instructions (Pollo et al., 2001) and conditioning trials (Colloca et al., 2010). These manipulations are sufficient to change behavioural and neural responses to pain stimuli (Eippert et al., 2009).

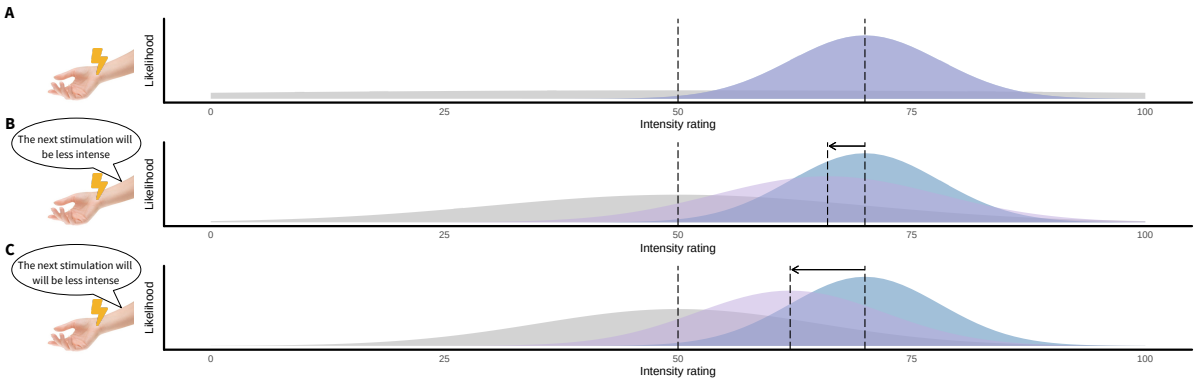


Figure 3.1: The effect of expectations on the placebo effect, modified from Buchel et al. (2014). The dashed lines indicate the mean stimulation levels of each distribution: prior, sensory evidence, and perception. (A) At the start of an experiment, participants have imprecise priors (grey distribution) of the incoming pain, as indicated by its wide distribution. This is because they are in a novel environment and have limited expectations. Their perception (purple distribution) therefore overlaps with the sensory evidence (blue distribution), and their perception is dominated by the sensory evidence. (B) During early phases of conditioning (through trials and verbal instructions), they form a prior that is more precise (grey distribution is less flat compared to A), and their perception (purple distribution) is influenced by both the prior and the sensory evidence. (C) Once the prior becomes more precise, the perception also becomes more precise, despite the sensory evidence remaining the same in terms of stimulation level and precision. The difference between sensory evidence and perception (as indicated by the arrows) is what is known as the placebo hypoalgesia effect. The more precise the prior, the greater the placebo hypoalgesia effect, as indicated by the longer arrow in C than in B.

Studies have shown that greater exposure to conditioning trials result in a stronger analgesic effect (Colloca et al., 2010). Under Bayesian accounts of perception (Büchel et al., 2014) this

is because a greater number of conditioning trials result in precise priors (lower uncertainty) despite large prediction errors (difference between the prior and sensory evidence), and these previous priors are combined with the sensory evidence to produce a percept that is less painful than the sensory evidence would otherwise produce (Büchel et al., 2014). In a typical placebo hypoalgesia paradigm, there are two phases: conditioning and placebo. In the conditioning phase, participants learn to associate cues with pain levels and build expectations about their pain experience. In the placebo phase, cues are still present but the associated sensory outcomes change. In the placebo phase, therefore, participants' perceived pain should be influenced by the expectation of upcoming pain according to the associations they built in the conditioning phase, if the conditioning was successful.

3.1.1 Goals and Hypotheses

The purposes of the study were to investigate i) whether the Bayesian account of autism is supported in pain perception, an interoceptive signal, and ii) if atypicality in the placebo hypoalgesia effect, which indicates atypical use or development of priors, is driven by autism or alexithymia. These goals are to test ideas that autistic perception is dominated by sensory evidence (Pellicano & Burr, 2012), and that interoceptive difficulties seen in autism are driven by alexithymic traits (Brewer et al., 2015). The three main variables of interest were the initial placebo effect as measured by the pain ratings and the anticipatory galvanic skin response (aGSR), and the extinction function. The extinction function is defined as the change in any placebo effect across trials after the conditioning procedure has been discontinued.

It was hypothesised that alexithymic traits, rather than autistic traits, will have an effect on the magnitude of the initial placebo effect (as measured by pain ratings and aGSR), and also on the extinction function. An effect on the extinction function was hypothesised, as Lawson et al. (2017) found that autistic individuals overestimate environmental volatility, and the extinction function is an indicator of how a large prediction error in the placebo phase (i.e., reflective of environmental volatility) is incorporated into perception. It was also hypothesised that placebo effect susceptibility will be determined by the precision of the expectations. For example, if the

expectations from the conditioning phase are precise, then the changes in the difference between the pain relief conditions (i.e., one trial type indicating some pain relief, while the other does not) during the placebo phase will be gradual. This will produce an extinction function that is stable as participants undertake more placebo trials.

3.2 Methods

3.2.1 Common Methods

For the rest of this thesis, similar recruitment strategies were employed, as listed below.

Participants

To ensure that there was a sufficient range of autistic and alexithymic traits in the study sample, a four-group setup was constructed for recruitment purposes: autistic participants with alexithymia (aut+alex), autistic participants without alexithymia (aut-alex), alexithymic participants without autism diagnoses (alex) and neurotypical participants (nt). Autistic participants who scored above 61 on the 20-item Toronto Alexithymia Scale (TAS-20; cut-off for alexithymia according to Bagby et al., 1994) were assigned to the aut+alex group, and autistic participants who scored below this cut-off (TAS-20 < 61) were assigned to the aut-alex group. Participants who met the cut-off on the TAS-20, but did not have an autism diagnosis, were assigned to the alex group. The nt group consisted of participants who had no current or recent psychiatric diagnoses or prescriptions of psychotropic medications and did not meet the cut-off on the TAS-20. Autism status was determined by the presence or absence of a formal diagnosis, not AQ-50 score.

All autistic participants had received a clinical diagnosis of autism or Autism Spectrum Disorder (ASD) from an independent clinician according to the DSM-IV or DSM-V (American Psychiatric Association, 2013). Autistic participants underwent Autism Diagnostic Observation Schedule Edition 2, Module 4 (ADOS-2; Lord et al., 2000) in a separate study session, whereby ADOS-2 scores were collected to quantify autistic traits. Participants with autism and

alexithymia were recruited from a database held at the Department of Experimental Psychology, University of Oxford. Other participant recruitment strategies included posting on social media, the departmental participant recruitment systems (SONA and OPR), and posters placed in cafés, libraries, and colleges.

Participant inclusion criteria

Participants were invited to take part in the study if they met the following inclusion criteria: i) fluent in English, ii) had normal or corrected-to-normal vision, iii) no heart or chronic pain conditions, iv) aged between 18 and 50, and v) agreed to refrain from using any analgesics on the day of the study. An upper age limit was set to minimise the effect of age-related change in pain perception (Lautenbacher et al., 2005).

Questionnaire measures

The following measures were used to quantify various traits of interest.

Autism Spectrum Quotient (AQ-50) The AQ-50 is a self-report questionnaire to quantify autistic traits, consisting of 50 items (Baron-Cohen et al., 2001). Each item (e.g., "I notice patterns in things all the time.") is rated on a 4-point Likert scale (definitely/slightly agree/disagree). A score of 32 or higher is strongly suggestive of a potential autism diagnosis (Baron-Cohen et al., 2001), though self-report AQ scores (both 10-item AQ and 50-item AQ) were found to be inadequate predictors of autism diagnosis (Ashwood et al., 2016).

20-item Toronto Alexithymia Scale (TAS-20) The TAS-20 is a self-report questionnaire to quantify alexithymic traits, consisting of 20 items (Bagby et al., 1994). Each item (e.g., "I have physical sensations that even doctors don't understand") is rated on a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree). A cut-off score of 61 suggests clinically-significant alexithymia. It has a three-factor structure, including sub-scales of i) difficulty describing feelings, ii) difficulty identifying feelings, and iii) externally-oriented thinking.

Spielberger State/Trait Anxiety Inventory (STAI) STAI is a self-report questionnaire to quantify anxious traits. STAI-1 quantifies state anxiety, and STAI-2 quantifies trait anxiety, both consisting of 20 items (Spielberger et al., 1983). Each item (e.g., "I feel calm" for STAI-1, "I am a steady person" for STAI-2) is rated on a 4-point Likert scale (STAI-1: 1 = not at all, 4 = very much so; STAI-2: 1 = almost never, 4 = almost always).

Beck Depression Inventory (BDI-II) The BDI-II is a self-report questionnaire designed to quantify depressive traits, consisting of 21 items (Beck et al., 1996). Each item (e.g., "I have not lost interest in other people or activities.) is rated on a 4-point Likert scale. The BDI-II asks participants about their depressive symptoms over the past two weeks and includes a suicidality item.

Pain Catastrophising Scale (PCS) PCS is a self-report questionnaire to quantify the degree to which one catastrophises pain, consisting of 13 items (Sullivan et al., 1995). Each item (e.g., "I worry all the time about whether the pain will end") is rated on a 5-point Likert scale (0 = not at all, 4 = all the time). A score above 30 is considered to be clinically relevant level of catastrophising (Sullivan et al., 1995). Pain catastrophisation is conceptualised as having three components that assess how one i) ruminates about one's pain, ii) magnifies one's pain, and iii) feels helpless to manage one's pain.

Body Perception Questionnaire (Short Form), Awareness sub-scale (BPQs-A) The BPQs-A is a self-report questionnaire to quantify bodily awareness, consisting of 26 items (Porges, 1993). Each item (e.g., "During most situations I am aware of how hard my heart is beating") is rated on a 5-point Likert scale (0 = never, 4 = always).

Interoceptive Accuracy Scale (IAS) IAS is a self-report questionnaire to quantify interoceptive accuracy, consisting of 21 items (Murphy et al., 2020). Each item (e.g., "I can always accurately perceive when my heart is beating fast") is rated on a 5-point Likert scale (1 = disagree strongly, 5 = strongly agree).

Interoceptive Attention Scale (IATS) IATS is a self-report questionnaire to quantify interoceptive attention, consisting of 21 items (Gabriele et al., 2022). Each item (e.g., "Most of the time my attention is focused on whether my heart is beating fast") is rated on a 5-point Likert scale (1 = disagree strongly, 5 = strongly agree). Using both IAS and IATS allows the quantification of beliefs about interoceptive accuracy and attention (Murphy et al., 2019)

Intolerance of Uncertainty Scale (IUS-12) IUS-12 is a self-report questionnaire to quantify intolerance of uncertainty, defined as negative beliefs about uncertainty and its consequences, consisting of 12 items (Wilson et al., 2020). Each item (e.g., "I must get away from all uncertain situations.") is rated on a 5-point Likert scale (1 = not at all characteristic of me, 5 = entirely characteristic of me).

Full Scale Intelligence Quotient (FSIQ) FSIQ was estimated using the vocabulary and matrix reasoning sub-tests of the Wechsler Abbreviated Scale of Intelligence (Second Edition, WASI-II; Wechsler, 2011). The vocabulary sub-test involved participants giving definitions of words, with 3 practice trials and 27 main trials. The matrix reasoning sub-test, consisting of 2 practice trials and 30 main trials, involved a series of visual puzzles with one missing part, and participants were asked to select one of the five options that fit the missing part the best. Both sub-tests increased in difficulty on every trial. The task ended once three consecutive incorrect responses were recorded. WASI-II was administered to test for differences in the level of cognitive functioning across groups.

Interpretation of scores Total scores were used for all questionnaires, except for BPQs-A and FSIQ, where T-scores were used. T-scores were calculated using appropriate standard conversion tables. For all questionnaires, higher scores indicate a higher level of the trait being assessed.

Electrical stimulation and calibration

Pain stimuli consisted of 200 μsecond square wave electrical pulses delivered using a Digitimer DS7A device with a bar electrode attached to the right inner wrist. Stimulation levels

were individually calibrated. Participants were given low levels of stimulation, increasing in small increments until the target pain level was found.

3.2.2 Participants

Participants were recruited under the pretence of a trial investigating the analgesic properties of transcutaneous electrical nerve stimulation (TENS). After the experiment, they were debriefed and made aware of the study objectives. The study was approved by the University of Oxford, Medical Sciences Interdivisional Research Ethics Committee, and all participants received an honorarium. Two studies using the same experimental paradigm were conducted. For analysis, participants from both studies were combined to provide a larger sample.

Study 1

34 adults (2 alex, 32 nt), recruited via the departmental participant recruitment system (SONA) participated in the study. This data set is from a previous study, utilising the same experimental paradigm, with the aim of looking at the individual differences in autistic and alexithymic traits in a neurotypical sample.

Study 2

77 adults (16 aut+alex, 18 aut-alex, 14 alex, 29 nt) participated in the study. For recruitment details, see Section 3.2.1.

Participant exclusion criteria

Participants were removed from analyses if they met any of the following criteria: i) unable to reach pain level 6 (out of 10) during the calibration, ii) were aware of the placebo-nature of the study, iii) did not discriminate between TENS-on (pain relief) and TENS-off (no pain relief) trials in the conditioning phase (mean pain ratings between trial types is less than 10 on the visual analogue scale (VAS), which is scaled to 100), and iv) had incomplete (self-report questionnaires) or faulty (GSR) data. After applying the exclusion criteria outlined above, the

composition of the final analysis sample can be found in 3.1. Further details on the exclusion process can be found in Section A.2.1.

Table 3.1: Summary of participants. Initial sample and final sample used for analyses after applying the exclusion criteria are listed. Participants were asked to identify their gender from three options: male, female, and other.

		Final sample			
Group	Initial sample	*N*	Mean ± SD age	Age range	Gender composition
aut+alex	16	12	32.5 (10.4)	[19.0, 48.0]	4 male, 7 female, 1 other
aut-alex	18	16	33.6 (9.46)	[19.0, 46.0]	8 male, 6 female, 2 other
alex	16	13	22.4 (4.44)	[18.0, 30.0]	3 male, 10 female
nt	61	55	26.5 (5.93)	[18.0, 42.0]	18 male, 37 female
Overall	111	96	27.9 (7.91)	[18.0, 48.0]	33 male, 60 female, 3 other

Analysis sample Prior to analyses, any statistical outliers (third quartile ± 1.5 × inter-quartile range) for three variables of interest were removed. This resulted in different sample size per variable of interest, per analysis. The composition of analysis sample per variable of interest can be found in Table 3.2.

Table 3.2: Analysis sample for variables of interest (initial placebo effect:rating, extinction function, initial placebo effect:aGSR) according to analysis type. placebo:rating: initial placebo effect:rating, extinct function: extinction function, placebo:aGSR: initial placebo effect:aGSR. Participants were removed prior to group comparisons if they were statistical outliers (third quartile ± 1.5 × inter-quartile range). In addition to outlier removal, for GAM analysis, participants were removed if they had incomplete questionnaire data, resulting in different number of participants depending on analysis and variable types.

Group	Initial sample size	Group comparisons			GAM analysis		
		placebo:rating	Extinct function	Initial placebo effect:aGSR	placebo:rating	Extinct function	placebo:aGSR
aut+alex	12	12	11	12	12	11	12
aut-alex	16	16	15	12	16	15	12
alex	13	12	12	10	12	12	10
nt	55	55	52	47	52	50	45
Overall	96	95	90	81	92	88	79

3.2.3 Measures and Procedure

Questionnaire measures

The following self-report questionnaires were used to assess how various traits affect the magnitude of the placebo hypoalgesia experienced: AQ-50 (autistic traits; Baron-Cohen et al., 2001), TAS-20 (alexithymic traits; Bagby et al., 1994), STAI-1, and STAI-2 (state and trait anxiety; Spielberger et al., 1983), BDI-II (depressive traits; Beck et al., 1996), PCS (pain

catastrophising; Sullivan et al., 1995), and BPQs-A (bodily awareness; Porges, 1993). For Study 2, WASI-II (cognitive intelligence; Wechsler, 2011) was also administered to obtain FSIQ. For details, see Section 3.2.1.

Electrical stimulation and calibration

The calibration procedure as outlined in Section 3.2.1 was used. Target stimulation was set as 6 out of 10 ("definitely uncomfortable, but tolerable") on a verbally reported pain scale, which was thereafter described as 100% or high pain level for that participant. Pain levels were explained as follows: 0 as "no pain," 6 as "uncomfortable, but tolerable", and 10 as "worst imaginable pain." The low pain stimulation was selected by using the intensity corresponding to 60% of the high pain level, a similar degree of reduction used in previous placebo hypoalgesia studies (e.g., Au Yeung et al., 2014).

Physiological measures

GSR was measured using a BIOPAC MP 150 system, sampled at 1kHz with the Acqknowledge 4.0 software. GSR was measured in micro-Siemens (μS) from two electrodes placed on the interphalangeal joint of the index and middle fingers of the left hand, and a ground electrode placed above the pisiform bone.

Conditioned placebo hypoalgesia task

The conditioned placebo hypoalgesia task (Au Yeung et al., 2014) was explained to participants as a task aiming to assess the analgesic efficacy of TENS. TENS was never employed, but instead, two placebo electrodes were used, placed approximately 20 cm from the pain delivery electrode on participants' right forearm. Participants were told that they would receive painful stimulations similar to the ones they received during the pain calibration without (TENS-off) and with (TENS-on) activation of TENS. TENS-off trials, as indicated by a red cross preceding the stimulation, would not alter the pain experience, whereas TENS-on trials, as indicated by a green cross preceding the stimulation, should reduce the intensity of the pain experienced.

As shown in Figure 3.2, each trial began with the presentation of 4-6 second inter-trial interval, followed by the presentation of the red or green cross. As an attention check and to reinforce the conditioning, participants were asked to verbally identify the colour of the cross on each trial. Once the correct colour was named, the experimenter pressed a key and the cue was shown for an additional anticipation period (4-6 seconds). This was followed by stimulation delivery (0.2 seconds), a cool-down phase (4-6 seconds), and then a pain intensity rating screen. Participants rated pain intensity on a VAS: 0 was set as no pain, 50 as moderate pain, and 100 as the worst pain imaginable. The initial position of the cursor on the VAS was randomised at each trial, and the numerical values of the scale were not shown during the rating screen.

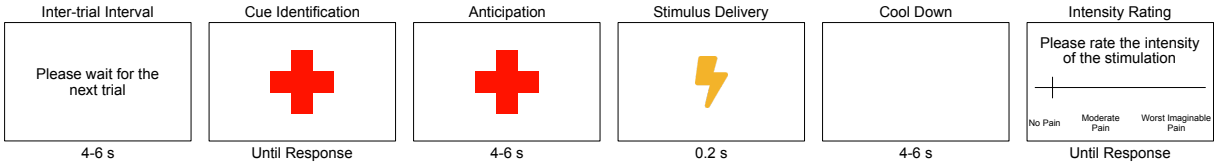


Figure 3.2: Conditioned placebo hypoalgesia task trial structure. A fixation cross indicating TENS activation (red: TENS-off; green: TENS-on) remained on the screen until the participant reported the cue colour. Cue identification was followed by an anticipation period (4-6 s), a stimulation delivery (0.2 s), a cool-down period (4-6 s), then an intensity rating screen. Intensity rating remained on the screen until the participant made a response. In between trials, participants had a resting period (4-6 s). The study consisted of 48 trials (24 trials per phase; 12 TENS-off/TENS-on).

Unbeknownst to the participants, the task was divided in 2 phases of 24 trials (12 trials each of TENS-off and TENS-on): conditioning and placebo. During the first phase, conditioning, TENS-off (red cross) trials delivered 100% stimulation level and TENS-on (green cross) trials delivered 60% stimulation level. During the second phase, placebo, which immediately followed the conditioning phase without any indication of transition, both TENS-off and TENS-on trials delivered 100% stimulation levels. Trials were intermixed in quasi-randomised order within participants, such that there were no more than three consecutive TENS-off or TENS-on trials. The first trial of the placebo phase was always a TENS-on trial, always followed by a TENS-off trial. The experimental task was presented using the Psychophysics Toolbox 3 (Brainard, 1997; Kleiner et al., 2007) within MATLAB (version 2015a; The MathWorks Inc., 2022)

Procedure

Prior to the experimental session, participants were asked to read the participant information sheet and complete demographic information, AQ-50, and TAS-20. At the experimental session, after giving informed consent, participants were seated in a quiet room. The study began with electrode placement (left hand: GSR electrodes; right arm: stimulation delivery device on the inner wrist, fake TENS device on the forearm), followed by pain calibration. Participants then completed the STAI-1 and took part in the conditioned placebo hypoalgesia task. Upon completion of the conditioned placebo hypoalgesia task, electrodes were removed. For Study 2 participants, WASI-II was administered next. Then, participants completed the STAI-2, BDI-II, PCS, BPQs-A, and a debriefing questionnaire assessing their awareness of the placebo manipulation. The conditioned placebo hypoalgesia task took approximately 20 minutes to complete, and the study session lasted approximately an hour for Study 1, and an hour and half for Study 2.

3.2.4 Statistical Analyses

All statistical analyses were performed using R (R Core Team, 2022) and RStudio (version 2023.06.0+421; RStudio Team, 2022), with a statistical threshold of $p < .05$.

Pain intensity ratings

The cursor position on the VAS was converted to a 0 (no pain) to 100 (worst pain imaginable) scale for each trial. Two dependent variables were derived from the pain intensity ratings: i) the initial placebo effect, and ii) the extinction function.

The initial placebo effect The initial placebo effect was calculated for each participant as the difference between the first TENS-off placebo trial (red cross followed by a 100% stimulation) and the first TENS-on placebo trial (green cross followed by a 100% stimulation). The placebo phase always started with a TENS-on trial (trial 13 of that trial type, trial 25 overall), followed by a TENS-off trial (trial 13 of that trial type, trial 26 overall), and so these two trials were

used to compute the initial placebo effect. This variable will be referred to as initial placebo effect:rating.

A value of 0 indicates the absence of a placebo effect (i.e., TENS-off and TENS-on trials perceived as being equal in pain intensity), positive values indicate the presence of placebo effect (i.e, TENS-off trial perceived as more painful than TENS-on trial), and negative values indicate the presence of nocebo effect (i.e., TENS-off trial perceived as less painful than TENS-on trial).

Extinction function An extinction function was derived for each participant using generalised additive models (GAM) due to the non-linear relationship between the difference between TENS-off and TENS-on trials (1-12) during the placebo phase. Estimated degrees of freedom (edf), which indicates the complexity of the relationship (e.g., edf of 1 is equivalent to a linear relationship, edf of 2 is equivalent to a quadratic relationship), was used as a proxy measure of the extinction function for each participant. The shape of extinction, rather than its rate, was measured as none of the participants achieved full extinction (i.e., the difference between TENS-off and TENS-on trials was never maintained at 0).

Group differences (aut+alex, aut-alex, alex, nt groups) in i) the initial placebo effect:rating, and ii) the extinction function were compared using Kruskal-Wallis test as the variables were not normally distributed even after transformation. Post-hoc Dunn's test using Bonferroni corrections were also used, where appropriate.

Galvanic skin response data

GSR data were bandpass filtered between 0.5 and 5Hz and the anticipatory GSR (aGSR) quantified by taking the peak value during the 4-second period before the stimulation delivery (anticipation). Each response was log transformed after the addition of a constant (1) to reflect the inherent skewness of the GSR. These were then z-scored within each participant using responses from all trials. Similar to the initial placebo effect:rating, the difference in z-scored aGSR between the first TENS-off placebo trial (red cross followed by a 100% stimulation) and the first TENS-on placebo trial (green cross followed by a 100% stimulation) was computed per participant. This variable will be referred to as the initial placebo effect:aGSR. One-way

ANOVA was then employed to assess whether there were any group differences (aut+alex, aut-alex, alex, nt groups) in the initial placebo effect:aGSR.

Generalised additive model

GAMs were employed to assess i) the difference in pain perception between TENS-off and TENS-on trials during the conditioning phase, and ii) whether any effects of autism or alexithymia on the placebo variables (initial placebo effect:rating, extinction function, and initial placebo effect:aGSR) survived after accounting for covariates. GAM was used as non-linear relationships between dependent and predictor variables were observed. GAM analyses were conducted using mgcv package (Wood, 2011), using the restricted maximum likelihood (REML) method. The best fit model was chosen based on the lower Akaike information criterion (AIC) and larger R^2 values. The summary of GAMs used in the present study is shown in Table 3.3.

Table 3.3: Description of GAMs. GAM-conditioning checked whether necessary conditions for the conditioning effect were met. GAM-trait had three types: GAM-trait:placebo_rating, which had initial placebo effect:rating as the dependent variable, GAM-trait:extinction, where the dependent variable was the extinction function, and GAM-trait:placebo_aGSR, where the dependent variable was initial placebo effect:aGSR. GAM-trait models assessed the effect of all self-report measures on the placebo variables. GAM-conditioning compared three models, GAM-trait compared four models for the best model fit.

Model			Dependent variable	**Terms**		
Name	Number	Type		Parametric	Smooth	Random effects
GAM-conditioning	1	Simple	Pain intensity rating	Cue (TENS-on, TENS-off), group	Conditioning trials (12)	
	2	Participant random				Participants
	3	Participant-cue random				Interaction between participants and cue
GAM-trait:placebo_rating GAM-trait:extinction GAM-trait:placebo_aGSR	1	Simple	Initial placebo effect:rating Extinction function Initial placebo effect:aGSR		Age, AQ-50, TAS-20	
	2	Simple-covariate			Age, AQ-50, TAS-20, STAI-1, STAI-2, BDI-II, PCS, BPQs-A	
	3	Interaction			Age, AQ-50*TAS-20	
	4	Interaction-covariate			Age, AQ-50*TAS-20, STAI-1, STAI-2, BDI-II, PCS, BPQs-A	

GAM-conditioning model The first analysis, GAM-conditioning model, looked at pain intensity ratings on a trial-by-trial basis during the conditioning phase (trial 1-12), to confirm the necessary requirements for the conditioning effect. Three GAM-conditioning models were compared for the best model fit, with the following terms. Model 1 (simple) had parametric terms of cue (TENS-on, TENS-off), group (aut+alex, aut-alex, alex, nt), and a smooth term of conditioning trials (1-12). Model 2 (participant random), in addition to model 1 terms, had an added random effects term of participants. Model 3 (participant-cue random) had the same terms as model 1 with an added random effects term of the interaction between participants and

cue.

GAM-traits models The second analysis, GAM-traits model, was conducted to determine whether autistic and alexithymic traits, as measured by AQ-50 and TAS-20 respectively, were significant predictors for the placebo variables (GAM-trait:placebo_rating – initial placebo effect:rating, GAM-trait:extinction – extinction function, GAM-trait:placebo_aGSR – initial placebo effect:aGSR) after including all control variables (age, STAI-1, STAI-2, BDI-II, PCS, and BPQs-A). Four GAM-traits models were compared for the best model fit per variable, resulting in 12 models. The smooth terms in the model were as follows: model 1 (simple) included age, AQ-50 and TAS-20 only, model 2 (simple-covariate) included all self-report questionnaire measures (age, AQ-50, TAS-20, STAI-1, STAI-2, BDI-II, PCS, and BPQs-A), model 3 (interaction) included AQ-50 and TAS-20 interaction and age, and model 4 (interaction-covariate) included AQ-50 and TAS-20 interaction with all other self-report questionnaire measures. FSIQ scores were not included as a term in the analysis as Study 1 participants did not complete the WASI-II, and no group difference in FSIQ was observed (see Section 3.3.1). Age was included as a control term in all models as there was group difference in age between nt and aut-alex groups.

3.3 Results

3.3.1 Descriptive Statistics

Table 3.4 summarises the demographic information for Studies 1 and 2 participants combined. To summarise, there were some group differences in the self-report measures. The autism groups (aut+alex and aut-alex groups) had a higher number of autistic, alexithymic, anxious (state and trait) and depressive traits than the nt group. The aut+alex group had higher autistic traits than the alex group. The aut-alex group was younger and had greater bodily awareness than the nt group. As expected, alexithymia groups (aut+alex and alex groups) had more alexithymic traits than non-alexithymia groups (aut-alex and nt groups). The alex group

had higher autistic, and depressive traits than the nt group. A detailed statistical summary can be found in Section A.2.2.

Table 3.4: Descriptive statistics for self-report measures. Study 1 participants did not complete the WASI-II, and therefore missing proportion of FSIQ is indicated. * $p < .05$, ** $p < .01$, *** $p < .001$.

	aut-alex n = 16	aut-alex n = 12	alex n = 13	nt n = 55	Overall N = 96
Age					
Mean (SD)	33.6 (9.46)	32.5 (10.4)	22.4 (4.44)	26.5 (5.93)	27.9 (7.91)
Median [Min, Max]	35.5 [19.0, 46.0]	31.0 [19.0, 48.0]	21.0 [18.0, 30.0]	26.0 [18.0, 42.0]	26.0 [18.0, 48.0]
	Comparisons: * nt < aut-alex				
Gender					
Male	8 (50.0%)	4 (33.3%)	3 (23.1%)	18 (32.7%)	33 (34.4%)
Female	6 (37.5%)	7 (58.3%)	10 (76.9%)	37 (67.3%)	60 (62.5%)
Other	2 (12.5%)	1 (8.3%)	0 (0%)	0 (0%)	3 (3.1%)
AQ-50					
Mean (SD)	33.9 (7.95)	41.4 (5.35)	27.2 (8.42)	16.3 (7.60)	23.8 (12.1)
Median [Min, Max]	34.0 [18.0, 44.0]	42.5 [26.0, 46.0]	25.0 [19.0, 47.0]	14.0 [2.00, 33.0]	22.5 [2.00, 47.0]
	Comparisons: *** alex < aut+alex, *** nt < aut+alex, *** nt < aut-alex, *** nt < alex				
TAS-20					
Mean (SD)	46.2 (9.70)	73.1 (4.85)	67.8 (7.20)	38.3 (8.55)	47.9 (15.9)
Median [Min, Max]	49.0 [28.0, 57.0]	73.0 [67.0, 85.0]	66.0 [61.0, 82.0]	37.0 [24.0, 60.0]	44.5 [24.0, 85.0]
	Comparisons: *** aut-alex < aut+alex, *** aut-alex < alex, *** nt < aut+alex, * nt < aut-alex, *** nt < alex				
STAI-1					
Mean (SD)	39.1 (10.4)	44.2 (13.3)	36.5 (12.4)	31.1 (7.10)	34.8 (10.4)
Median [Min, Max]	38.5 [21.0, 63.0]	42.0 [24.0, 67.0]	30.0 [26.0, 66.0]	31.0 [20.0, 51.0]	34.0 [20.0, 67.0]
	Comparisons: ** nt < aut+alex, * nt < aut-alex				
STAI-2					
Mean (SD)	52.7 (10.3)	58.8 (13.0)	51.9 (10.6)	37.8 (12.2)	44.8 (14.3)
Median [Min, Max]	52.5 [29.0, 74.0]	57.5 [32.0, 75.0]	54.0 [31.0, 69.0]	38.0 [0, 55.0]	46.0 [0, 75.0]
	Comparisons: ** nt < aut+alex, * nt < aut-alex				
BDI-II					
Mean (SD)	17.5 (13.4)	21.3 (18.3)	15.4 (9.56)	6.09 (6.21)	11.1 (11.7)
Median [Min, Max]	15.5 [0, 37.0]	16.0 [0, 55.0]	15.0 [4.00, 31.0]	5.00 [0, 24.0]	7.00 [0, 55.0]
	Comparisons: ** nt < aut+alex, ** nt < aut-alex, ** nt < alex				
PCS					
Mean (SD)	16.1 (9.60)	24.6 (13.8)	19.8 (11.8)	15.4 (10.6)	17.3 (11.3)
Median [Min, Max]	13.0 [0, 32.0]	25.0 [1.00, 47.0]	18.0 [2.00, 38.0]	14.0 [0, 48.0]	15.0 [0, 48.0]
BPQs-A					
Mean (SD)	57.5 (11.0)	55.5 (10.1)	55.0 (6.12)	49.9 (10.3)	52.5 (10.3)
Median [Min, Max]	55.3 [45.8, 78.7]	59.6 [28.0, 63.7]	54.7 [46.9, 66.5]	48.3 [28.0, 72.3]	52.0 [28.0, 78.7]
	Comparisons: * nt < aut-alex				
FSIQ					
Mean (SD)	123 (12.3)	114 (9.85)	125 (12.3)	116 (11.4)	119 (12.1)
Median [Min, Max]	125 [97.0, 148]	115 [96.0, 128]	121 [105, 150]	117 [90.0, 135]	120 [90.0, 150]
Missing	0 (0%)	0 (0%)	2 (15.4%)	30 (54.5%)	32 (33.3%)
Stimulation level					
Mean (SD)	30.7 (19.1)	30.8 (22.5)	32.2 (23.2)	37.9 (25.7)	35.0 (23.9)
Median [Min, Max]	26.0 [8.50, 65.0]	23.0 [12.0, 90.0]	22.0 [5.00, 88.0]	36.0 [1.45, 99.9]	30.0 [1.45, 99.9]

3.3.2 Confirmation of the Differences in the Conditioning Phase

Average pain intensity ratings, extinction function shown as pain intensity rating difference, and average z-score transformed aGSR are shown in Figure 3.3.

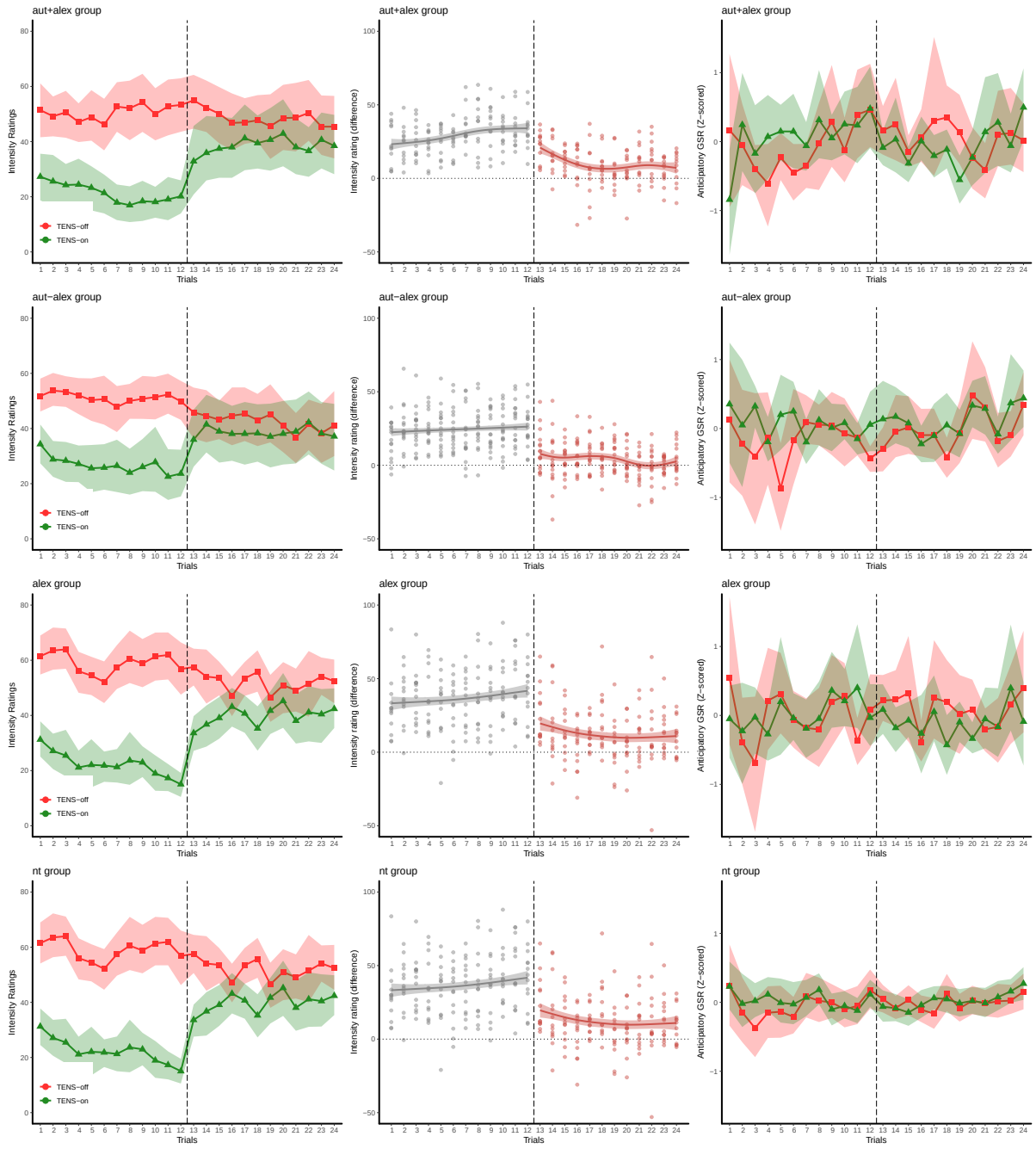


Figure 3.3: Pain ratings (left), pain rating difference (middle), and aGSR (right) as a function of trial (1-24) per group. The dashed vertical lines indicate the start of the placebo phase (trial 13-24), and the shaded regions represent the 95% confidence interval. (Left) Mean pain ratings as a function of trial and cue type. (Middle) Extinction function shown as the mean intensity rating difference between TENS-off and TENS-on trials as a function of trial. The dotted line indicate where the difference between TENS-off and TENS-on trials is 0, meaning an absence of placebo effect. (Right) aGSR as a function of trial and cue type.

A GAM-conditioning model was fit to trial-by-trial data in the conditioning phase. Comparison between the three GAM-conditioning models showed that model 2 (participant random), which accounts for individual differences in pain intensity ratings was the best model fit [AIC = 17600.83, adjusted R^2 = .753]. An effect of cue [estimate = 29.11, $p < .001$] was found, meaning that participants perceived, on average, the stimulation following TENS-off cue as more painful than the stimulation following the TENS-on cue. There was also an effect of trials [edf = 2.65, $p < .001$] and participants [edf = 89.03, $p < .001$]. No group effects were found, where nt group was used as the reference: i) aut+alex group [estimate = -1.39, p = .721], ii) aut-alex group [estimate = 1.50, p = .668], and iii) alex group [estimate = 3.24, p = .391]. Thus, the necessary requirements for the conditioning to take place were established (a difference in perceived pain between TENS-off and TENS-on trials) and the degree of this difference did not vary as a function of group. The relationship between cues (TENS-off, TENS-on) and trials in the conditioning and the placebo phase are shown in Figure 3.4.

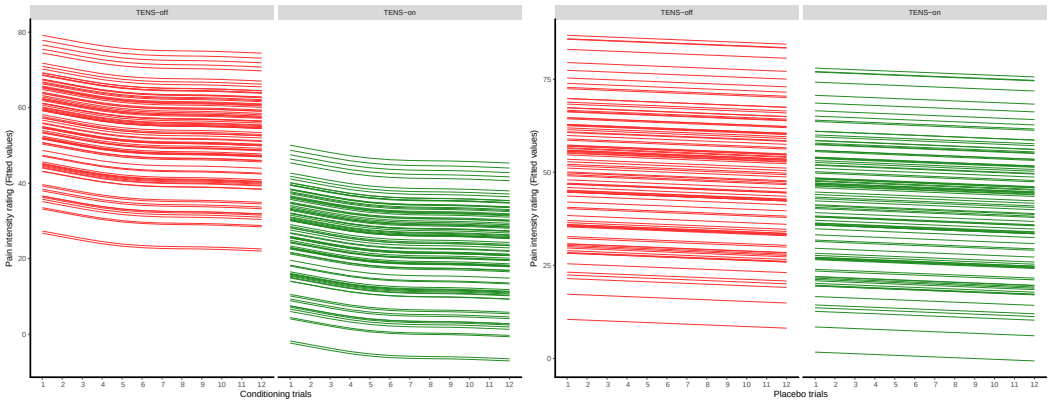


Figure 3.4: Relationship between fitted pain intensity ratings across trials per cue. Pain ratings are shown across trials for (left) the conditioning phase, and (right) the placebo phase. Red indicates TENS-off, and green indicates TENS-on trials. In the conditioning and the placebo phase, there was an effect of cue and trials, where participants viewed pain stimulations following TENS-off (red) trials as more painful than those after TENS-on trials (green).

3.3.3 Group Comparisons of Placebo Effect Variables

Kruskal-Wallis tests were performed to determine whether there were any significant group differences in the initial placebo effect:rating, and the extinction function. One-way ANOVA was performed to assess any significant group differences in the initial placebo effect:aGSR.

Group comparisons for each variable are illustrated in Figure 3.5, and group mean values can be found in Table 3.5.

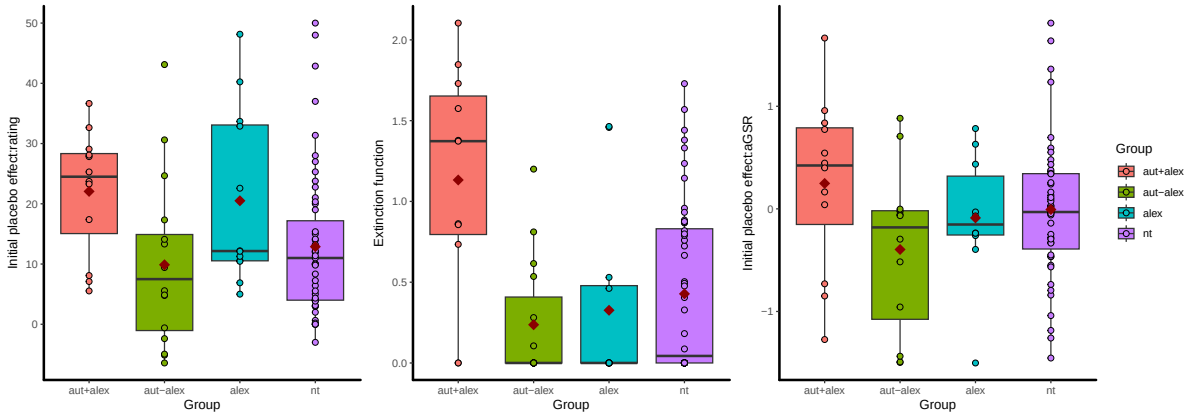


Figure 3.5: Group comparisons of the placebo variables: (left) initial placebo effect:rating, (middle) extinction function, and (right) initial placebo effect:aGSR. Group comparisons showed significant differences between the aut-alex and aut+alex groups for intial placebo effect:rating and extinction function. There were also significant differences in extinction function between the aut+alex and alex groups, and the aut+alex and nt groups. No significant effect of group was found for initial placebo effect:aGSR.

Table 3.5: Group means of placebo variables (initial placebo effect:rating, extinction function, and initial placebo effect:aGSR). Participant sample size differ depending on the variable, as statistical outliers were removed prior to analyses.

	aut+alex	aut-alex	alex	nt	Overall
Initial placebo effect:rating					
N	12	16	12	55	95
Mean (SD)	22.1 (10.3)	9.88 (13.9)	20.5 (14.6)	12.9 (12.1)	14.5 (13.0)
Median [Min, Max]	24.5 [5.53, 36.6]	7.49 [-6.43, 43.1]	12.2 [5.00, 48.1]	11.0 [-3.00, 50.0]	12.0 [-6.43, 50.0]
Extinction function					
N	11	15	12	52	90
Mean (SD)	1.13 (0.707)	0.237 (0.379)	0.326 (0.563)	0.428 (0.522)	0.469 (0.584)
Median [Min, Max]	1.37 [8.47x10^{-5}, 2.10]	7.84x10^{-5} [3.94x10^{-5}, 1.20]	6.96x10^{-5} [2.85x10^{-5}, 1.46]	4.35x10^{-2} [1.51x10^{-5}, 1.73]	4.36x10^{-2}[1.51x10^{-5}, 2.10]
Initial placebo effect:aGSR					
N	12	12	10	47	81
Mean (SD)	0.248 (0.843)	-0.396 (0.809)	-8.82x10^{-2} (0.643)	-6.42x10^{-3} (0.682)	-3.65x10^{-2} (0.731)
Median [Min, Max]	0.423 [-1.27, 1.67]	-0.181 [-1.50, 0.883]	-0.152 [-1.50, 0.783]	-3.06x10^{-2} [-1.45, 1.81]	-3.06x10^{-2} [-1.50, 1.81]

Initial placebo effect (rating)

There was a statistically significant group effect on the initial placebo effect:rating [$\chi^2(3) = 10.91$, $p = .012$]. Post-hoc Dunn's test revealed that the initial placebo effect:rating was smaller for the aut-alex group than the aut+alex group [$Z = -2.74$, $p = .037$]. This means that the aut-alex group rated the first placebo trials of TENS-off and TENS-on more similarly than the aut+alex group. Other pair-wise comparisons were not significant.

Extinction function

There was also a statistically significant effect of group on the extinction function [$\chi^2(3)$ = 13.44, p = .004]. Dunn's test revealed that the extinction function was significantly less complex (e.g., more linear than a quartic curve) for i) the aut-alex group than the aut+alex group [Z = -3.26, p = .007], ii) the alex group than the aut+alex group [Z = -3.12, p = .011], and iii) the nt group than the aut+alex group [Z = -3.11, p = .011]. Other pair-wise comparisons were not significant. Plots of extinction function per participant can be found in Figure A.3.

Initial placebo effect (aGSR)

Group differences in the initial placebo effect:aGSR was assessed next, and no statistically significant group difference was found [$F(3)$ = 1.66, p = .183].

3.3.4 Individual Differences in Placebo Effect Variables

GAM analyses were employed to determine whether alexithymic and autistic traits could predict the initial placebo effect:rating, the extinction function, and the initial placebo effect:aGSR, once self-report measures were taken into account.

Simple correlations

Simple correlations of all variables can be found in Table 3.6. As expected, many of the self-report measures were correlated with one another. In particular, AQ-50 and TAS-20 were highly correlated (r = .785, $p < .001$). None of the placebo variables (initial placebo effect:rating, extinction function, initial placebo effect:aGSR) were correlated with any of the self-report questionnaires.

Effects of Self-Report Measures on Placebo Effect Variables

Significant relationships between self-report questionnaire measures and placebo variables are shown in Figure 3.6.

Table 3.6: Simple correlations between self-report measures and placebo variables. AQ-50: autistic traits, TAS-20: alexithymic traits, STAI-1: state anxiety, STAI-2: trait anxiety, BDI-II: depressive traits, PCS: pain catastrophising trait, BPQs-A: bodily awareness. * $p < .05$, ** $p < .01$, *** $p < .001$.

	Age	AQ-50	TAS-20	STAI-1	STAI-2	BDI-II	PCS	BPQs-A	Initial placebo effect:rating	Extinction function
Age										
AQ-50	.236									
TAS-20	-.224	.785**								
STAI-1	.022	.375	.485							
STAI-2	-.061	.657*	.671*	.672*						
BDI-II	.004	.517	.547	.670*	.789**					
PCS	-.201	-.015	.159	.586	.338	.379				
BPQs-A	-.031	.318	.094	-.002	.377	.154	.206			
Initial placebo effect:rating	-.510	-.222	.123	-.241	-.389	-.160	-.120	-.201		
Extinction function	-.074	-.285	-.100	-.133	-.276	-.022	-.158	-.429	.301	
Initial placebo effect:aGSR	-.334	-.419	-.345	-.447	-.304	-.355	-.416	-.426	-.138	.075

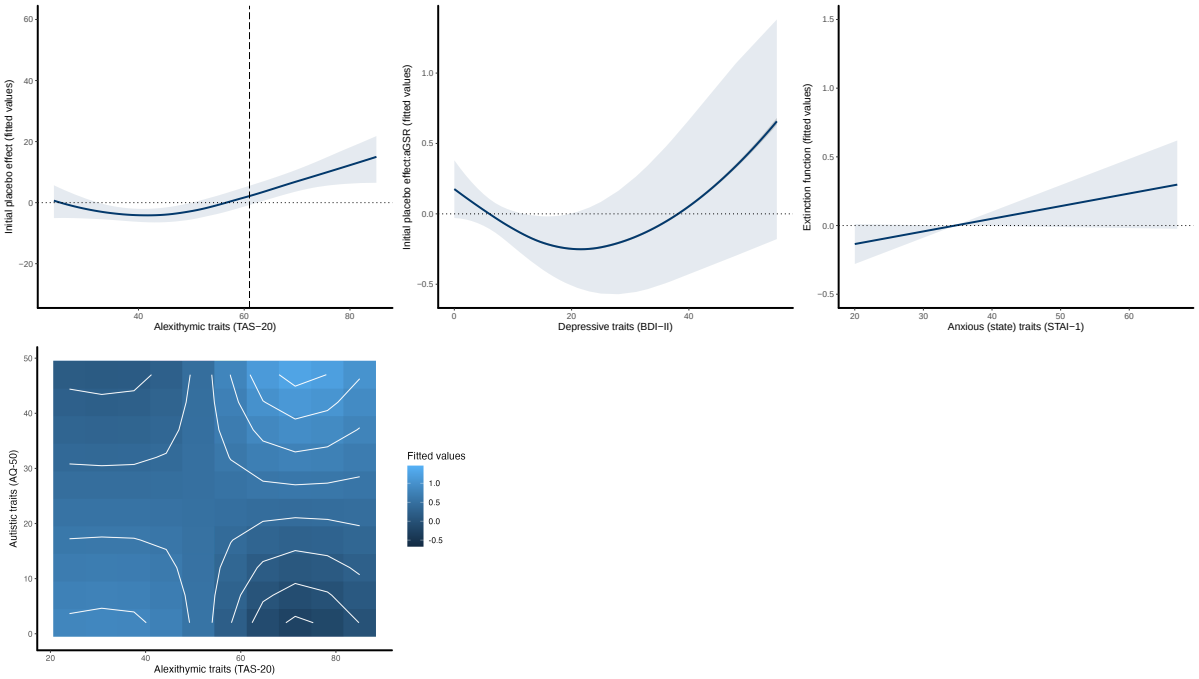


Figure 3.6: Relationships between significant self-report predictors and fitted values of placebo variables from GAM-traits models. Top: (left) a quadratic relationship between TAS-20 and the initial placebo effect:rating, (middle) a quadratic relationship between BDI-II and the initial placebo effect:aGSR, (right) a linear relationship between STAI-1 and the extinction function. Bottom: A quadratic relationship between AQ-50 and TAS-20 interaction term and the extinction function. The shaded area represents the 95% confidence interval.

Effects on the initial placebo effect (rating) GAM-traits:placebo_rating model was performed to assess the effect of self-report measures on the initial placebo effect:rating. Comparison between four GAM-traits:placebo_rating models found that model 2 (simple-covariate) which included all self-report measures (age, AQ-50, TAS-20, STAI-1, STAI-2, BDI-II, PCS, and BPQs-A) as smooth terms was the best model fit for the initial placebo effect:rating [AIC = 708.05, adjusted R^2 = .191]. TAS-20 [edf = 2.15, $p < .001$] was the only significant predictor of the magnitude of the initial placebo effect:rating. The relationship between TAS-20 and

the initial placebo effect:rating was a U-shaped curve, whereby the size of the initial placebo effect:rating decreases as the alexithymic trait increases, until the initial placebo effect size starts increasing again. For clinically-relevant levels of alexithymia (TAS-20 $\geq$ 61), the relationship is approximately linear, where the higher the alexithymic trait, the bigger the initial placebo effect:rating (i.e., TENS-off is rated as more painful than TENS-on on the first placebo trial, despite both trials delivering the same stimulation level). No effect of AQ-50 [edf = 3.02×10^{-5}, p = .215] was found.

As an exploratory analysis, initial placebo effect:aGSR was added as a smooth term to model 1 (simple) and model 3 (interaction) to see if the alexithymia effect was mediated by higher anticipation, as indicated by initial placebo effect:aGSR. Model 1 (simple) which included age, AQ-50, TAS-20, and initial placebo effect:aGSR as smooth terms was the best model fit [AIC = 612.74, adjusted R^2 = .196]. TAS-20 remained significant [edf = 2.10, $p < .001$], and other terms were not significant: age [edf = 5.3×10^{-4}, p = .332], AQ-50 [edf = 5.80×10^{-5}, p = .595], and initial placebo effect:aGSR [edf = 0.441, p = .184].

Effects on the extinction function GAM-traits:extinction model was performed to assess the effect of self-report measures on the extinction function. Comparison between four GAM-traits:extinction models found that model 2 (interaction-covariate), which included all self-report measures as smooth terms with AQ-50 and TAS-20 interaction as smooth terms was the best model fit [AIC = 145.69, adjusted R^2 = .195]. AQ-50 and TAS-20 interaction term [edf = 2.59, $p < .001$] and STAI-1 [edf = 0.767, p = .035] were significant predictors for the extinction function. For the AQ-50 and TAS-20 interaction, the higher both the scores, the more complex the extinction function. Having high alexithymic traits but low autistic traits also led to a more complex extinction function. For STAI-1, it was a linear relationship where the higher the state anxiety, the more complex the extinction function.

Effects on the initial placebo effect (aGSR) GAM-traits:placebo_aGSR model was performed to assess the effect of self-report measures on the inital placebo effect:aGSR. Comparison between four GAM-traits:placebo_aGSR models found that model 2 (simple-covariate), which

included all self-report measures (age, AQ-50, TAS-20, STAI-1, STAI-2, BDI-II, PCS, and BPQs-A) as smooth terms was the best model fit [AIC = 175.75, adjusted R^2 = .099]. BDI-II [edf = 1.77, p = .018] was the only significant predictor for the initial placebo effect:aGSR. This was a U-shaped relationship, where the initial placebo effect:aGSR became smaller with an increase in depressive traits, until the relationship reverses around a BDI-II score of 25. For BDI-II scores of 40 or above, aGSR is greater in the first trial of TENS-off than in the first trial of TENS-on. No effects of AQ-50 [edf = 3.27×10^{-5}, p = .897] or TAS-20 [edf = 3.30×10^{-5}, p = .779] were found.

3.4 Discussion

The present study investigated whether the degree of placebo hypoalgesia exhibited in a pain perception paradigm was affected by either autistic or alexithymic traits. This was intended to allow testing of two separate hypotheses. First, to allow testing of the Bayesian account of autism (Pellicano & Burr, 2012) in the novel context of the interoceptive domain. Second, to allow testing of the alexithymia hypothesis (Brewer et al., 2015), which outlines that any atypicality in emotional or interoceptive perception in autism would be explained by alexithymia, not autism.

There were no group differences in the pain ratings in the conditioning phase, which suggests the paradigm worked as intended for all groups. The initial placebo effect, as measured by pain intensity ratings, was observed across all groups. All groups provided higher ratings for TENS-off trial compared to TENS-on trial at the beginning of the placebo phase. Thus, participants successfully formed expectations about upcoming pain according to the cue type (TENS-off, TENS-on), and these expectations influenced their pain perception. This study adds to a large body of existing studies showing that verbal instructions and conditioning are sufficient to change behavioural responses to pain stimuli (Colloca et al., 2010; Pollo et al., 2001).

With respect to the magnitude of the placebo effect computed from pain intensity ratings, the placebo effect was greater in the autism with alexithymia (aut+alex) group than in the autism without alexithymia (aut-alex) group. When analysed after accounting for all measured covariates with GAM analysis, the effect of alexithymia was significant, and no effect of autism

was found.

The lack of an effect of autism means that the Bayesian account of autism was not supported by these data. If it was the case that autistic perception was governed more by sensory evidence than expectations about upcoming pain, one would have expected to see a reduced placebo effect in autism. Instead, the magnitude of the placebo effect was not significantly impacted by the presence or absence of an autism diagnosis, or by autistic traits. This adds to an already mixed literature, with some studies finding support for the Bayesian account (Goris et al., 2018; Lawson et al., 2017) and some not (Manning et al., 2017; Tewolde et al., 2018). However, this is the first time that the Bayesian account of autism has been explored in the interoceptive domain. It is possible that the Bayesian account of autism does not hold in either the interoceptive or exteroceptive domain, or in the interoceptive domain only, and further work is needed to distinguish between these possibilities.

This study was able to unconfound the effects of autism and alexithymia, which is necessary as the two conditions show a high rate of co-occurrence (meaning that previous studies comparing a group of autistic participants with a neurotypical control group are likely to have confounded autism and alexithymia). The results of this study are not able to test the alexithymia hypothesis directly, however, as that hypothesis states that the effects of autism on interoceptive or emotional perception are actually due to co-occurring alexithymia. Here, no effect of autism was found, and so the hypothesis cannot be directly tested. There was an effect of alexithymia on the initial placebo effect, such that the size of the initial placebo effect increased with greater levels of alexithymia. However, this is opposite to the effect predicted by the Bayesian account of autism. Therefore, co-occurring alexithymia cannot explain previously observed effects that are consistent with the Bayesian account of autism.

The observed effect of alexithymia is consistent with previous reports linking alexithymia with inaccurate perception of interoceptive signals (Brewer et al., 2016; Cuve et al., 2021; P. Shah et al., 2016). It is possible that alexithymic individuals learn to place less weight on their interpretation of the sensory evidence as it is frequently inaccurate and instead rely on external cues, such as the information that the TENS device would reduce pain. More precise priors could explain the greater placebo effect observed with increasing alexithymia, however,

it remains unclear whether there is also a greater influence of those priors on perception.

Analysis of the extinction function, which assessed the change in the placebo effect over trials and whether this varied as a function of group, indicated a main effect of alexithymia, not autism. There was also an interaction between autism and alexithymia. This manifested such that the extinction function was close to 0 for all participants, except for participants who were both autistic and had high levels of alexithymia. An extinction function of 0 indicates that the placebo effect did not change across trials, and it remained relatively constant for all groups except autistic participants with alexithymia (aut+alex group). Despite the association between cues and outcomes remaining stable during the placebo phase, there is a big change in the association between the TENS-on cue and the level of pain from the conditioning to the placebo phase. Thus, one aspect involved in the extinction function is the degree to which the initial prediction error for the TENS-on cue is incorporated in the following expectations during the placebo phase. The increased complexity of the extinction function in autistic participants with alexithymia suggests a noisier, and slower, learning effect over the placebo trials. Further work is required to confirm this, however, as the extinction function is not solely a product of learning rate.

One limitation of the study is that the multiple co-occurring conditions seen in several participants are not accounted for, and neither are the medications taken mostly by autistic and alexithymic participants. Many of the medications taken affect neurotransmitters (see Table A.6), such as noradrenaline for anti-anxiety, antidepressant and stimulant medications. The Bayesian inference framework suggests the involvement of many neuromodulatory transmitters, such as glutamate in prediction error modulation (Friston, 2005), acetylcholine in priors suppression (Yu & Dayan, 2005), and noradrenaline in volatility learning (Marshall et al., 2016). Studies have found all of the neurotransmitters listed above – glutamate (Horder et al., 2018), acetylcholine (Sokol et al., 2002) and dopamine (Lawson et al., 2017) – to be dysregulated in autism, so it is not unusual that many participants take pharmacological treatments. Accounting for the medication taken, and any effect on Bayesian frameworks would be ideal, as asking participants to refrain from taking their medication is arguably unethical, and also would not remove any longer-term effects of the medication. It is not ideal to exclude autistic and alexithymic participants who take

medications, as it would make the sample unreflective of the general autistic and alexithymic population.

In summary, this study does not provide evidence for the Bayesian account of autistic perception. Given that no effects of autism were found, the alexithymia hypothesis could not be directly tested, but results were consistent with the hypothesis that alexithymia is associated with imprecise and inaccurate perception of interoceptive cues, which increased the effect of priors in this group. Further studies are needed to investigate the effect of prediction error on perception and learning, and how these may be affected by autism and alexithymia.

Chapter 4

Effects of prediction error size and valence on pain perception

Abstract

The magnitude and the valence of prediction error, the mismatch between a prior expectation and sensory evidence, are important factors in shaping one's pain perception. It was recently demonstrated that the magnitude and valence of prediction errors affect the degree of influence of the prior expectation on perception. When the magnitude of the prediction error is large (beyond the "tipping point"), then one's perception becomes more accurate and less affected by one's expectation than when prediction errors are smaller, but the point at which this happens is also influenced by whether the delivered pain was more or less painful than expected (i.e., the valence of prediction error). The present study used a paradigm whereby different levels of prediction errors were elicited. The study investigated whether the impact of prediction errors was modulated by i) the magnitude of the prediction error, ii) the valence of the prediction error, and iii) individual differences in autistic and alexithymic traits. Results showed that, in line with the previous study, the magnitude and the valence of prediction error impacted pain perception. Autism modulated this effect, but it was alexithymia, not autism, that modulated how this effect changed over the course of the task.

4.1 Introduction

It is clear that expectation influences pain perception. There exists extensive evidence supporting the modulation of perceived pain by expectation, such as nocebo and placebo effects (Colloca & Benedetti, 2006; Colagiuri et al., 2015), as well as the results from Chapter 3. A recent study by Hird et al. (2019) showed that while expectation is an important factor that modulates pain perception, the extent to which it influences perception changes with different magnitudes of prediction error. Hird et al. (2019) propose that there exists a "tipping point," whereby the influence of expectation on perception becomes smaller (and thus the influence of sensory evidence becomes greater) as the size of prediction error increases.

An illustration of the tipping point theory can be found in Figure 4.1, which demonstrates the relationship between prediction error and subjective error.

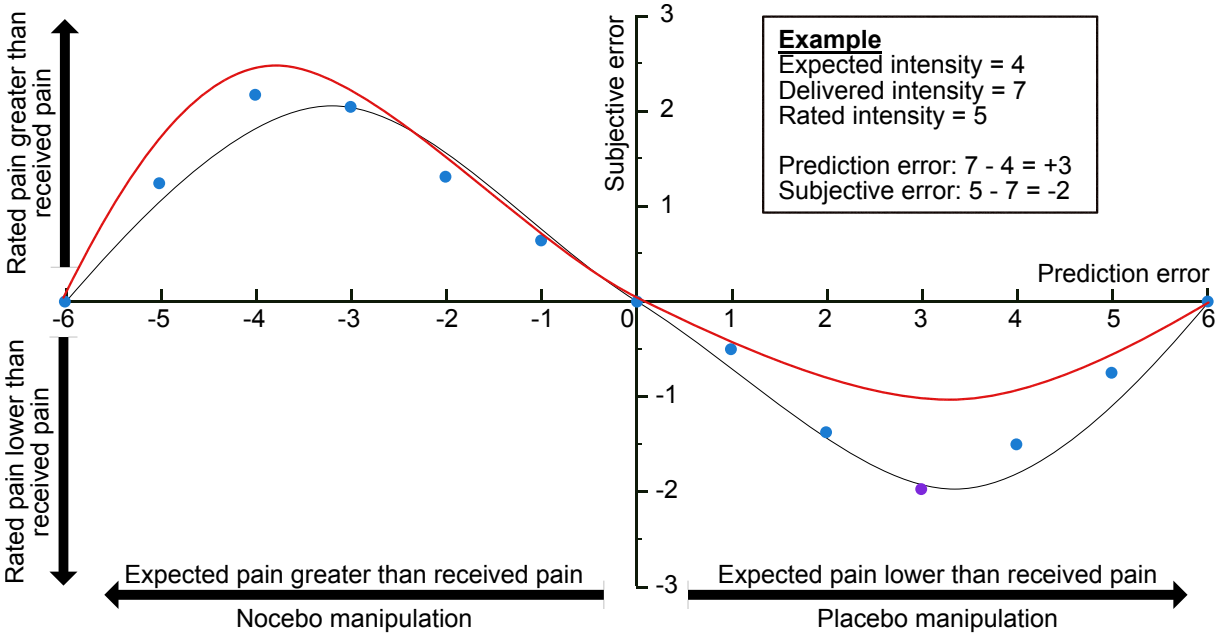


Figure 4.1: Tipping point theory, modified from Hird et al. (2019). The graph shows the expected relationship between prediction error and subjective error. Prediction error is the difference between delivered and expected pain intensity, while subjective error is the difference between rated and delivered pain intensity. The tipping point theory stipulates that there exists a point at which prediction error is too large for the expectation to be considered useful, and therefore the expectation has less of an influence on perception, such as when the prediction error is ± 5 and ± 6. An example of a scenario is depicted in the box, with the corresponding data point shown in purple in the lower right quadrant. Illustration is reflective of the research proposing that placebo effects were more easily extinguished than nocebo responses, as in the perception was less influenced by expectation when the prediction error was positive, rather than negative. The black curve illustrates a quartic curve not influenced by valence, and the red curve illustrates hypothetical results showing a valence effect on the quartic function (indicative of the tipping point).

Prediction error is the difference between the delivered and expected pain intensity, and sub-

jective error is the difference between perceived and delivered pain. For example, if participants are shown a cue indicating that an upcoming pain stimulation will be level 4 intensity, but are given level 7, they will have a prediction error of +3. If they are influenced by the cue, they would rate the stimulation as less painful than it actually was as a result of the placebo effect, such as 5. Their subjective error would therefore be -2, as subjective error is an indicator of the extent to which the perception was influenced by the cue, and therefore by the expectation.

The idea of the tipping point is that prediction errors above a certain size result in a reduced influence of expectation on perception. The degree of modulation is likely influenced by both the size and valence (positive or negative) of prediction errors. Modulation of the influence of expectation on perception when faced with a prediction error is essential, especially in the context of learning (Den Ouden et al., 2012; S. S. Y. Li & McNally, 2014). It is not only necessary to know that the prior is inaccurate, but in which direction the prior needs to be updated. Indeed, a failure to adjust the influence of expectation may result in inaccurate perception, such as hallucinations observed in psychosis (Sterzer et al., 2018).

Previous studies suggest that influence of prediction errors on perception varies as a function of their valence. For example, nocebo effects are more difficult to extinguish than placebo effects (Au Yeung et al., 2014; Colagiuri et al., 2015), suggesting that the degree of influence the prior has on perception differs depending on the prediction error valence (i.e., whether it is a placebo or nocebo effect). In addition, there is significant evidence showing that anxiety amplifies pain perception (Colloca & Benedetti, 2007; Rooney et al., 2022). Indeed, Hird et al. (2019) propose that the placebo effect is more sensitive to factors such as learning and individual differences in personality traits than nocebo effects, in line with previous literature (Colloca & Miller, 2011; Geers et al., 2007; Wager & Atlas, 2015).

4.1.1 Goals and Hypotheses

The present study aimed to provide the first replication of the study by Hird et al. (2019) to determine the evidence for the tipping point – the point at which prediction errors become so large that their effect on perception is reduced. It was also sought to determine whether

the influence of priors on perception varies according to the valence of the prediction error, and according to individual differences. In particular, the study focused on whether individual differences in autistic and alexithymic traits explained the differences in influence of priors on perception, based on the Bayesian account of autism (Pellicano & Burr, 2012) and the alexithymia hypothesis (Brewer et al., 2015). Any potentially confounding personality traits, such as anxiety, depression, and interoceptive accuracy, were also measured to assess how each factor may contribute to the tipping point, and the influence of expectations on perception more generally.

Given the findings of Chapter 3, it was hypothesised that alexithymic traits, rather than autistic traits, will modulate the influence of expectations on perception and therefore the tipping point (if it is replicated). It was hypothesised that subjective error will be modulated by the precision of the expectations that are updated throughout the task (as participants realise that cues are not always veridical). Based on the results from Chapter 3 which showed that alexithymic traits shape the mechanisms behind prediction formation and updating during pain perception, it was hypothesised that the quartic curve indicative of a tipping point will be modulated by alexithymic traits, rather than autistic traits.

4.2 Methods

4.2.1 Participants

83 adults (19 aut+alex, 16 aut-alex, 13 alex, 35 nt) participated in the study. Participant recruitment and inclusion criteria were as outlined in Section 3.2.1. Participants were recruited to take part in a study looking at pain perception in autism and alexithymia. After the experiment, they were debriefed and made aware of the study objectives. The study was approved by the University of Oxford, Medical Sciences Interdivisional Research Ethics Committee, and all participants received an honorarium.

Participant exclusion criteria

Participants were removed from analyses if they met any of the following criteria: i) did not meet the inclusion criteria, ii) unable to pass calibration, and iii) had incomplete questionnaire data. The participant sample for each group before and after the application of exclusion criteria are shown in Table 4.1.

The final analysis sample, after applying the exclusion criteria, consisted of 76 adults (39 female, 8 other; age 25.7 ± 9.65). The composition of the final analysis sample can also be found in Table 4.1.

Table 4.1: Analysis sample composition after the application of exclusion criteria, which were as follows: i) did not meet the inclusion criteria, ii) failed the pain calibration, and iii) had incomplete questionnaire data. Participants were asked to identify their gender from three options: male, female, and other.

Group	Initial sample	Exclusion criteria			Final analysis sample			
		i	ii	iii	*N*	Mean ± SD age	Age range	Gender composition
aut+alex	19	0	1	0	18	31.5 ± 11.4	[18, 49]	10 male, 6 female, 2 other
aut-alex	16	0	1	0	15	27.9 ± 11.5	[18, 48]	7 male, 3 female, 5 other
alex	13	0	0	0	13	21 ± 5.21	[18, 34]	12 female, 1 other
nt	35	1	3	1	30	23.2 ± 7.00	[18, 45]	12 male, 18 female
Total	83	1	5	1	76	25.7 ± 9.65	[18, 49]	29 male, 39 female, 8 other

4.2.2 Measures and Procedure

Questionnaire measures

The following self-report questionnaires were used to assess various traits: AQ-50 (autistic traits; Baron-Cohen et al., 2001), TAS-20 (alexithymic traits; Bagby et al., 1994), STAI-1, and STAI-2 (state and trait anxiety; Spielberger et al., 1983), BDI-II (depressive traits; Beck et al., 1996), PCS (pain catastrophising; Sullivan et al., 1995), BPQs-A (bodily awareness; Porges, 1993), IAS (interoceptive accuracy; Murphy et al., 2020), IATS (interoceptive attention; Gabriele et al., 2022), IUS-12 (intolerance of uncertainty; Wilson et al., 2020), and WASI-II (cognitive intelligence; Wechsler, 2011) to obtain FSIQ. For details, see Section 3.2.1.

Electrical stimulation and calibration

The calibration procedure outlined in Section 3.2.1 was used. Target stimuli were pain levels 2 through 8 out of 10 on a verbally reported numerical pain scale (NPS). NPS 2 was described as "just painful", NPS 5 was "medium pain", and NPS 8 was "just tolerable," as in previous research (Hird et al., 2019). NPS 2 through 8 were then delivered in a pseudo-randomised order and participants were instructed to identify the intensity of each stimulation. The process continued until the participants were consistent in their ratings at least twice in a row.

Prediction error size task

The prediction error size task (Hird et al., 2019) was explained to participants as a task where the cue, which was a number, predicted the upcoming stimulus intensity. Unbeknownst to the participants, not all cues were veridical predictors of the upcoming pain level. Cues 3 through 7 were veridical cues, which meant that the cue always accurately indicated the upcoming pain stimulation level, and therefore the prediction error was always 0. These cues reinforced participants' beliefs that the cues were, in fact, veridical, and were 50% of the total trials (60 trials total). Cues 2 and 8, on the other hand, were not always veridical predictors of the upcoming pain level, and a range of prediction errors were elicited. After seeing cues 2 or 8, participants could receive any of the possible stimulation levels (i.e., levels 2, 3, 4, 5, 6, 7, or 8) with the same probability across all blocks. This meant that for cue 2, prediction errors ranged from 0 to 6, whereas for cue 8, they ranged from 0 to -6.

As shown in Figure 4.2, participants first viewed a fixation cross for a second, followed by a number ranging from 2 to 8 which was the cued intensity for that trial. After an anticipation period of 4-6 seconds, participants received the stimulus for 0.2 seconds, followed by a cool-down period of 4-6 seconds. A rating screen was then shown, where participants were asked to rate the pain on a scale from 0 to 10. The rating screen remained on the screen until participants were satisfied with their response and indicated that they were ready to go to the next trial. Descriptions of 0, 5 and 10 were presented on the scale, as "no pain," "moderate pain," and "worst pain imaginable," respectively. The initial position of the cursor on the scale

was randomised on each trial, and the numerical value of the chosen rating was indicated. Participants were asked to rate the stimulus intensity as they felt it, not as they would have thought to have felt it. The requirement to rate the pain was explained by stating that some people become more sensitive to pain, while others habituate to pain, after repeated stimulation, and therefore pain response may change over time. Participants were also told that some people do not experience changes in sensitivity, and that everyone experiences pain differently.

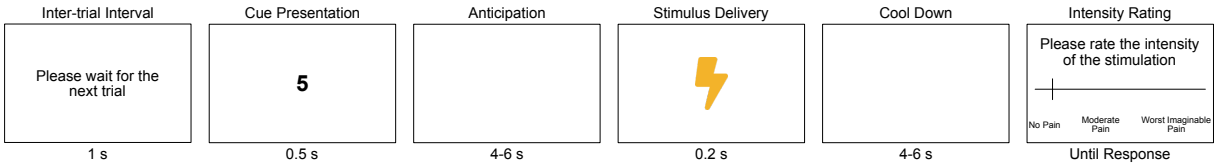


Figure 4.2: Prediction error task trial structure. After an inter-trial interval (1 s), a number predicting the upcoming pain stimulation level (2 through 8) was presented (0.5 s). This was followed by an anticipation period (4-6 s), stimulation delivery (0.2 s), and a cool-down period (4-6 s). Finally, a pain intensity rating scale was presented which remained on the screen until the participant made a response. The study consisted of 24 trials of 5 blocks, totalling 120 trials. Participants took self-timed breaks between blocks.

Trials were intermixed in a quasi-randomised order within participants, such that there were no more than three consecutive trials of the same type. Participants were presented with 6 practice trials prior to starting the main task, and were given the opportunity to ask any questions they might have had. The task consisted of 24 trials of 5 blocks, totalling 120 trials. Further details on the trial structure can be found in Section A.3.1. Participants took self-timed breaks between blocks. The experimental task was presented using PsychoPy (v2022.2.5; Peirce et al., 2019).

Procedure

Prior to the experimental session, participants were asked to read the participant information sheet and complete demographic information, AQ-50, TAS-20, BPQs-A, IAS, and IUS-12 questionnaires. At the experimental session, after giving informed consent and confirming their demographic information, participants were seated in a quiet room. The pain stimulation delivery device was then placed on the participant's right forearm. Pain calibration started immediately after to determine the necessary pain stimulation levels. Once the pain levels were chosen, participants completed the STAI-1 questionnaire, then took part in the prediction

error size task. Upon completion of the main task, electrodes were removed, and participants completed the WASI-II, STAI-2, BDI-II, PCS, and IATS. The prediction error size task took approximately 40 minutes to complete, and the study session lasted approximately two hours.

4.2.3 Statistical Analyses

All statistical analyses were performed using R (R Core Team, 2022) and RStudio (version 2023.06.0+421; RStudio Team, 2022), with a statistical threshold of $p < .05$.

Pain intensity ratings

For analyses, pain intensity ratings were taken per trial per participant. Trials were excluded from analyses if the experimenter was unable to change the stimulation level to the appropriate level in time for stimulation delivery. From pain intensity ratings, subjective error was calculated, which could range from -8 to +8 as the rating scale ranged from 0 to 10. Prediction error ranged from -6 to +6, as the cues ranged from 2 to 8. Prediction error could only be positive for any trials with cue 2, and could only be negative for any trials with cue 8. A few examples of trials are shown in Table 4.2.

Table 4.2: Examples of prediction errors and subjective errors. Prediction error could only range from -6 to +6. This is because cues and delivered stimulation levels were limited between 2 and 8. For subjective error, the range was bigger, between -8 to +8, as participants could rate stimuli between 0 and 10. When participants saw cue 2, prediction error could only be positive, and when participants saw cue 8, prediction error could only be negative.

	Cue	Delivered stimulation level	Rating	Prediction error	Subjective error
i)	2	8	0	+6	-8
ii)	8	2	10	-6	+8
iii)	2	5	0	+3	-5

Generalised additive models

The aim of the present study was to replicate Hird et al.'s (2019) analysis plan, where they conducted a non-linear mixed effects (NLME) model. NLME analysis method was preferred, as it provides more reliable predictions for the response variable outside the observed range of the data when compared to, for example, polynomial models (Pinheiro & Bates, 2000). It also uses

fewer parameters compared to a linear model, providing a more parsimonious description of the data (Pinheiro & Bates, 2000). However, before replicating Hird et al.'s (2019) NLME methods, it was first necessary to ensure that the analysis strategy adopted by them was appropriate for the present study. Therefore, generalised additive models (GAMs) were run prior to the NLME analyses to assess whether trends observed in Hird et al.'s (2019) data that led to the construction of their NLME model were also observed in the present study. These trends were also tested for autistic and alexithymic group effects. GAMs were employed as it was likely that the relationships being analysed would be non-linear.

GAMs were employed to test the assumptions made in Hird et al.'s (2019) NLME model. These were i) the presence of habituation (GAM-habituation), ii) the presence of a cue effect (GAM-cue), iii) the effect of prediction error size (GAM-pe_size), and iv) the effect of prediction error valence (GAM-pe_valence). GAM analyses were conducted using the mgcv package (Wood, 2011), using the REML method. The best fit model was chosen based on the lower AIC and larger R^2 values. The summary of GAM models is shown in Table 4.3.

Table 4.3: Description of GAMs to check the assumptions of the NLME model. GAM-habituation checked for the presence of a habituation effect, GAM-cue checked for the presence of a cue effect. GAM-pe_size checked for the effect of prediction error size on subjective error, and the two types of GAM-pe_valence (GAM-pe_valence:overall and GAM-pe_valence:individual) checked for the effect of prediction error size and valence on subjective error. Three models per analysis were compared for the best model fit. Trial in all models mean trial position (1-120). abs: absolute value.

	Model			**Terms**		
Name	Number	Type	Dependent variable	Parametric	Smooth	Random effects
GAM-habituation GAM-cue	1 2 3	Simple Participant random Participant-cue random	Pain intensity rating	Cue, autism group, alexithymia group	Trial (1-120)	 Participants Interaction between participants and cue
GAM-pe_size	1 2 3	Simple Participant random Participant-pe (abs) random	Subjective error (abs)	Autism group, alexithymia group	Subjective error (abs), trial (1-120)	 Participants Interaction between participants and prediction error (absolute value)
GAM-pe_valence:overall	1 2 3	Simple Participant random Participant-pe random	Subjective error (abs)	Autism group, alexithymia group	Prediction error, trial (1-120)	 Participants Interaction between participants and prediction error
GAM-pe_valence:individual	1 2 3	Simple Participant random Participant-pe random	Subjective error (abs)	Prediction error (factor), autism group, alexithymia group	Trial (1-120)	 Participants Interaction between participants and prediction error

In general, model 1 was the simplest model with the terms of interest. Model 2, in addition to model 1 terms, had a random effect of participants. Model 3, in addition to model 1 terms, had a random effect of the interaction between participants and the variable of interest (GAM-habituation and GAM-cue: cue, GAM-pe_size: absolute value of prediction error, GAM-pe_valence: prediction error). Trial in all models mean trial position (1-120).

GAM-habituation model Hird et al.'s (2019) NLME model assumes that pain perception changes across the course of the task, i.e., participants may show habituation. To assess whether this was also the case in the present study, GAM-habituation model was conducted to assess the habituation effect. This was run on trials with cues 3 through 7, as there were no prediction errors on these trials throughout the task. GAM-habituation was modelled across all cues. Three GAMs were compared for the best model fit, listed as models 1, 2 and 3 in Table 4.3. The dependent variable was pain intensity rating, with terms of cue, autism group (autism, non-autism), alexithymia group (alexithymia, non-alexithymia), trial (1-120), and where relevant, random effect terms of participants, and cue.

GAM-cue model After the confirmation of the habituation effect, it was necessary to confirm the presence of the cue effect, otherwise the remaining analyses would not have been meaningful. GAM-cue model was conducted to assess the cue effect on trials with cues 2 and 8, where the prediction error was greater than 0 (range: ± 1 to ± 5). This meant excluding trials where cues 2 and 8 were veridical cues. GAM-cue model was modelled separately per intensity level, to test whether there were any group differences in the cue effect at each level of the intensity. Three GAMs per five intensity levels (15 models total) were compared for the best model fit, and these are models 1, 2, and 3 listed in Table 4.3. The dependent variable was again pain intensity rating, with terms of cue, autism group (autism, non-autism), alexithymia group (alexithymia, non-alexithymia), trial (1-120), and where relevant, random effect terms of participants and cue.

GAM-pe_size model After confirming the presence of the cue effect, it was then necessary to first assess the effect of prediction error size alone, without considering its valence, on subjective error. GAM-pe_size model was performed to assess the effect of the absolute value of prediction error on the absolute value of subjective error, modelled across all levels of prediction error. Three GAMs were compared for the best model fit, and these are models 1, 2, and 3 listed in Table 4.3. The dependent variable was the absolute subjective error, with terms of absolute prediction error, autism group (autism, non-autism), alexithymia group (alexithymia, non-alexithymia), trial (1-120), and where relevant, random effect terms of participants and absolute value of

prediction error.

GAM-pe_valence models After confirming the effect of prediction error size, GAM-pe_valence models were performed to assess the effect of prediction error size and valence. Two types of GAM-pe_valence models were run with absolute value of subjective error as the dependent variable, as the valence of prediction error was of interest, not the valence of the subjective error. First, GAM-pe_valence:overall was modelled across all levels of prediction error, with smooth term of prediction error and trial (1-120). Second, GAM-pe_valence:individual was modelled per each level of prediction error size (i.e, ±1 to ±6) with prediction error as a factor term and smooth terms of trial (1-120), to assess if there were any differences in the effect of prediction error valence on subjective error depending on the magnitude of the prediction error size. Three GAM-pe_valence:overall, and three GAM-pe_valence:individual per six levels of prediction error size (18 models total) were compared for the best model fit, and are listed as models 1, 2, and 3 in Table 4.3.

Non-linear mixed effects model

Upon confirming the assumptions underlying the NLME analysis used by Hird et al. (2019) as outlined above in Section 4.2.3, NLME was performed to assess whether the modulation of subjective error (modulation of pain ratings by cue) was influenced by prediction error. NLME analysis was performed using nlme package (Pinheiro & Bates, 2000). The development of NLME models using Hird et al.'s (2019) methodology was followed, starting with a quartic polynomial prediction error term with a trial interaction as the starting model. First, three models were compared: i) a model without random effects, ii) a model with a random intercept, and iii) a model with a random intercept and a random slope of the polynomial prediction error terms. Second, the best model from the first step was then used to explore the best covariance matrix (unstructured, diagonal, compound symmetry, identity). Third, the best model from the second step was used to choose the best random error covariance matrix (compound symmetry structure, AR structure). And finally, the fourth step checked which fixed effects were important by removing certain fixed effects terms and comparing the model fit.

Upon replicating Hird et al.'s (2019) methodology outlined above, the same procedure with fixed effects of quartic polynomial prediction error terms and their trial interaction interacting with i) autistic traits, and ii) alexithymic traits were repeated. This step was performed to assess whether these two traits modulate the relationship between subjective error and prediction error.

Elastic net

Elastic net linear regression was used to assess whether the modulation of subjective error was influenced not only by prediction error, but also by other nuisance covariates. An elastic net approach was chosen due to the small sample size relative to the number of predictors and the high correlation among the self-report questionnaire measures. Elastic net analysis was conducted using glmnet (Friedman et al., 2010) and caret (Kuhn, 2008) packages, using the cross-validation method. All variables were centred prior to analysis. If the variables were not normally distributed, they were transformed according to the λ of the Box Cox transformation function (Box & Cox, 1964; log transformation was deemed appropriate for all since $-0.5 < \lambda < 0.5$), then centred. A constant of 1000 was added to all variables prior to log transformation to avoid getting negative infinity values. λ value was selected as the largest λ that gives the most regularised model, at which the mean of squared errors (MSE) is within 1 standard error of the smallest MSE.

Two types of elastic net regressions were run. In the first, the dependent variable was the subjective error, with independent variables of all self-report questionnaire measures, and polynomial terms of prediction error (PE, PE^2, PE^3, PE^4). As the present study is a repeated-measures paradigm, an average subjective error per prediction error per participant was used as the dependent variable, to avoid artificially inflating the degrees of freedom. This analysis was performed to confirm the findings of the GAM and NLME analyses. In the second, the dependent variables were random slopes of polynomial terms of prediction error from the NLME analysis (PE, PE^2, PE^3, PE^4), resulting in four models. The independent variables were all self-report questionnaire measures.

4.3 Results

4.3.1 Descriptive Statistics

Table 4.4 summarises the demographic information for all participants. Group comparisons found that the non-autism group compared to the autism group were younger, had less autistic and depressive traits, catastrophised pain less, and had lower interoceptive accuracy. The non-alexithymia group compared to the alexithymia group had lower scores in the following self-report scores: autistic traits, alexithymic traits, state and trait anxiety, depressive traits, pain catastrophising tendencies, and intolerance of uncertainty. Further details of group comparisons can be found in Section A.3.2.

Table 4.4: Descriptive statistics for self-report measures. * $p < .05$, ** $p < .01$, *** $p < .001$.

	Autism		**Non-autism**		**Overall**	
	Alexithymia $n = 18$	Non-alexithymia $n = 15$	Alexithymia $n = 13$	Non-alexithymia $n = 30$	Alexithymia $n = 31$	Non-alexithymia $n = 45$
Age						
Mean (SD)	31.5 (11.4)	27.9 (11.5)	21.0 (5.21)	23.2 (7.00)	27.1 (10.6)	24.8 (8.91)
Median [Min, Max]	26.0 [18.0, 49.0]	20.0 [18.0, 48.0]	19.0 [18.0, 34.0]	20.5 [18.0, 45.0]	21.0 [18.0, 49.0]	20.0 [18.0, 48.0]
	Comparisons: *** non-autism < autism					
Gender						
Male	10 (55.6%)	7 (46.7%)	0 (0.0%)	12 (40.0%)	10 (32.3%)	19 (42.4%)
Female	6 (33.3%)	3 (20.0%)	12 (92.3%)	18 (60.0%)	18 (58.1%)	21 (46.7%)
Other	2 (11.1%)	5 (33.3%)	1 (7.7%)	0 (0.0%)	3 (9.7%)	5 (11.1%)
AQ-50						
Mean (SD)	38.7 (5.64)	30.7 (7.61)	25.5 (8.88)	18.6 (6.89)	33.2 (9.69)	22.6 (9.13)
Median [Min, Max]	37.0 [31.0, 49.0]	32.0 [18.0, 40.0]	26.0 [12.0, 47.0]	17.0 [6.00, 34.0]	34.0 [12.0, 49.0]	20.0 [6.00, 40.0]
	Comparisons: *** non-autism < autism, *** non-alexithymia < alexithymia					
TAS-20						
Mean (SD)	67.5 (7.10)	48.1 (10.9)	68.7 (6.60)	42.3 (7.58)	68.0 (6.81)	44.2 (9.13)
Median [Min, Max]	65.5 [61.0, 91.0]	51.0 [21.0, 60.0]	66.0 [61.0, 82.0]	43.5 [27.0, 60.0]	66.0 [61.0, 91.0]	44.0 [21.0, 60.0]
	Comparisons: *** non-alexithymia < alexithymia					
STAI-1						
Mean (SD)	42.4 (11.4)	36.9 (12.7)	38.4 (8.17)	32.7 (9.26)	40.7 (10.2)	34.1 (10.6)
Median [Min, Max]	41.0 [25.0, 74.0]	36.0 [20.0, 60.0]	38.0 [23.0, 51.0]	33.0 [21.0, 59.0]	40.0 [23.0, 74.0]	34.0 [20.0, 60.0]
	Comparisons: * non-alexithymia < alexithymia					
STAI-2						
Mean (SD)	58.5 (6.35)	49.9 (12.9)	58.1 (9.59)	43.9 (10.2)	58.3 (7.73)	45.9 (11.4)
Median [Min, Max]	58.0 [44.0, 70.0]	54.0 [28.0, 67.0]	59.0 [31.0, 69.0]	45.5 [29.0, 64.0]	58.0 [31.0, 70.0]	47.0 [28.0, 67.0]
	Comparisons: *** non-alexithymia < alexithymia					
BDI-II						
Mean (SD)	16.8 (9.29)	12.7 (8.74)	15.9 (9.47)	6.33 (4.40)	16.5 (9.22)	8.47 (6.81)
Median [Min, Max]	18.0 [4.00, 38.0]	12.0 [0, 28.0]	14.0 [2.00, 36.0]	7.00 [0, 16.0]	17.0 [2.00, 38.0]	7.00 [0, 28.0]
	Comparisons: ** non-autism < autism; *** non-alexithymia < alexithymia					
PCS						
Mean (SD)	30.7 (8.69)	22.2 (11.1)	24.3 (12.9)	15.3 (10.5)	28.0 (11.0)	17.6 (11.1)
Median [Min, Max]	31.5 [16.0, 50.0]	24.0 [6.00, 41.0]	22.0 [5.00, 51.0]	13.5 [0, 43.0]	28.0 [5.00, 51.0]	16.0 [0, 43.0]
	Comparisons: *** non-autism < autism; ** non-alexithymia < alexithymia					
BPQs-A						
Mean (SD)	54.4 (7.46)	56.7 (9.16)	56.1 (6.31)	54.0 (8.92)	55.1 (6.94)	54.9 (8.99)
Median [Min, Max]	56.0 [39.3, 66.1]	57.5 [43.5, 75.3]	54.7 [49.6, 68.3]	55.8 [37.7, 79.7]	55.1 [39.3, 68.3]	55.8 [37.7, 79.7]
IAS						
Mean (SD)	57.1 (14.0)	64.6 (15.9)	66.8 (9.51)	72.0 (12.9)	61.2 (13.0)	69.6 (14.2)
Median [Min, Max]	55.5 [37.0, 82.0]	63.0 [39.0, 98.0]	67.0 [54.0, 86.0]	72.5 [46.0, 100]	61.0 [37.0, 86.0]	72.0 [39.0, 100]
	Comparisons: ** autism < non-autism					
IATS						
Mean (SD)	46.7 (11.8)	43.2 (14.5)	45.5 (11.2)	42.6 (13.2)	46.2 (11.4)	42.8 (13.5)
Median [Min, Max]	47.5 [22.0, 63.0]	41.0 [26.0, 80.0]	49.0 [30.0, 62.0]	40.0 [20.0, 81.0]	49.0 [22.0, 63.0]	40.0 [20.0, 81.0]
IUS-12						
Mean (SD)	43.4 (7.48)	36.5 (8.68)	42.2 (8.16)	33.4 (7.95)	42.9 (7.66)	34.4 (8.24)
Median [Min, Max]	45.0 [28.0, 54.0]	38.0 [18.0, 47.0]	44.0 [23.0, 52.0]	33.0 [13.0, 48.0]	45.0 [23.0, 54.0]	34.0 [13.0, 48.0]
	Comparisons: ** non-alexithymia < alexithymia					
FSIQ						
Mean (SD)	122 (15.8)	124 (15.6)	125 (12.1)	121 (10.9)	123 (14.2)	122 (12.6)
Median [Min, Max]	121 [91.0, 152]	127 [89.0, 150]	121 [106, 150]	121 [100, 144]	121 [91.0, 152]	121 [89.0, 150]

4.3.2 Confirmation of the Assumptions of NLME Model

Prior to conducting NLME analyses, several GAMs were run to confirm the assumptions made in the NLME analysis.

Confirmation of the habituation effect

First, the presence of a habituation effect was checked. The pain intensity ratings across trials for veridical cues (3, 4, 5, 6, 7) are shown in Figure 4.3. Comparison between the three GAM-habituation models showed that model 2 (participant random), which accounts for individual differences in pain intensity ratings, was the best model fit [AIC = 11550.18, adjusted R^2 = .687].

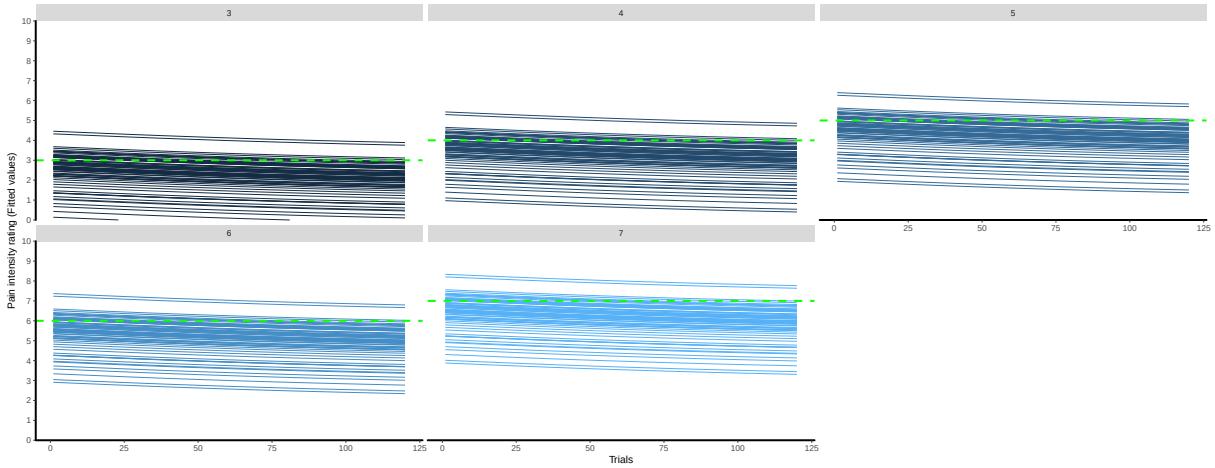


Figure 4.3: Confirmation of the habituation effect. Pain ratings are shown across trials (1-120) for the five veridical cues (top, left to right: 3, 4, 5; bottom, left to right: 6, 7). All trials shown are where the prediction error was 0. This means that what the cue indicated was the stimulation level participants received following the cue. Each line represents a participant, and the neon green dashed lines indicate the delivered stimulation intensity. There is a general trend of pain intensity ratings decreasing as the trials went on, suggestive of the presence of habituation. There was an effect of cue and trial number, where participants viewed pain stimulations following different cues differently, and across trials (1-120).

An effect of veridical cue [estimate = 0.969, $p < .001$] was found, meaning that participants perceived, on average, stimulations following five different cues (3, 4, 5, 6, 7) differently. This was expected, as these cues were veridical, and therefore the stimulation level differed between all cues. There was also an effect of trial [edf = 1.73, $p < .001$] and participants [edf = 70.84, $p < .001$]. The effect of trial is indicative of a pattern where participants, across trials, rated the stimulus as less painful despite receiving the same stimulation level. This observation could be

due to a number of factors, such as habituation to the stimuli or dampening of anxiety about the task (LeBlanc & Potvin, 1966). The presence of habituation confirmed the need to add trial (1-120) as terms in the rest of the GAM analyses. No effect of autism group [autism vs. non-autism: estimate = -0.125, p = .568] nor alexithymia group [alexithymia vs. non-alexithymia: estimate = 0.164, p = .456] were found.

Confirmation of the cue effect

Next, the presence of a cue effect needed to be tested. Average pain intensity ratings as a function of delivered stimulus intensity are shown in Figure 4.4.

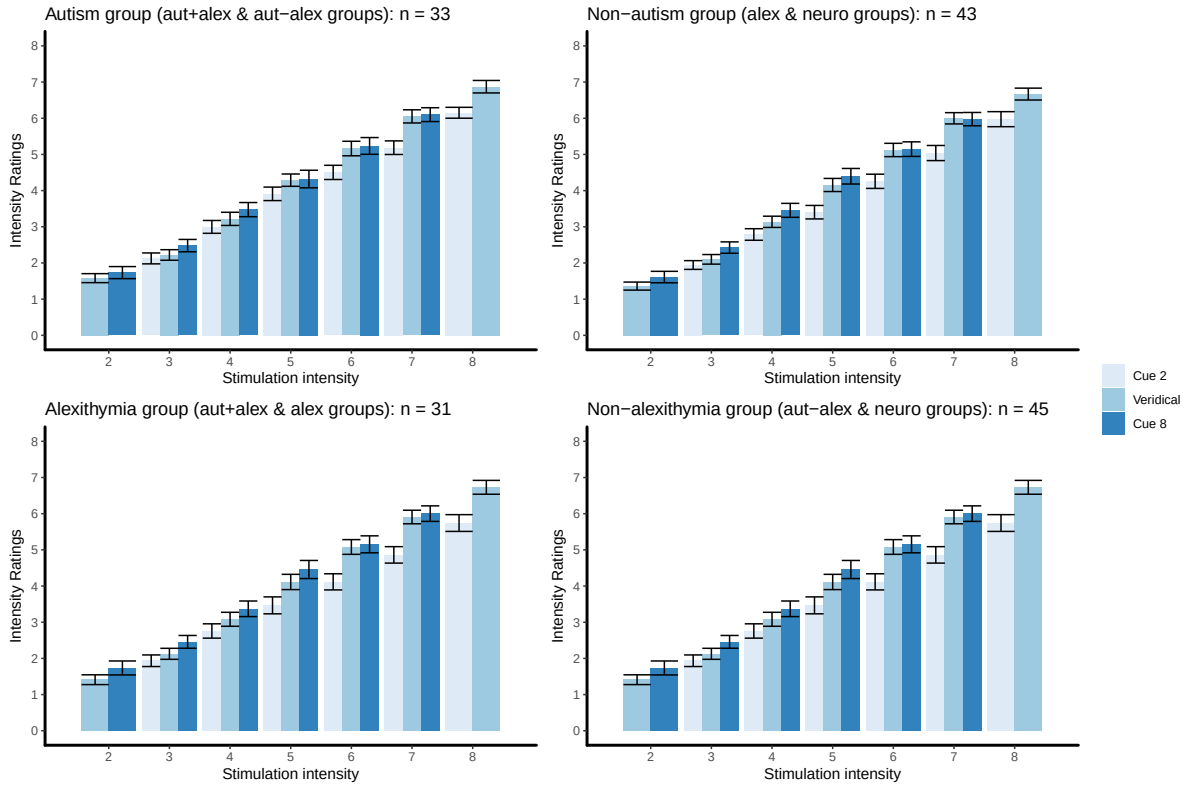


Figure 4.4: Average pain intensity ratings as a function of delivered stimulus intensity. Light blue bars are when participants saw cue 2, medium blue bars are when cues were veridical, and dark blue bars are when participants saw cue 8. Error bars represent the standard error of the mean. There is a trend of ratings increasing with an increase in delivered stimulation intensity. There is also a trend of stimulations after cue 2 being perceived less painful than those after cue 8, despite receiving the same stimulation intensity.

GAM-cue models were modelled for trials where cues 2 and 8 were shown and prediction error was greater than 0 (i.e., non-veridical cues). GAM-cue models were performed separately per intensity level (3 through 7) to see if there are group differences in the cue effect depending

on the intensity level. Trial (1-120) was added as a smooth term, due to the presence of habituation as presented in Section 4.3.2. Therefore, three GAM-cue models were performed for each intensity level being assessed, resulting in a total of 15 models. The best model fits were as follows. GAM-cue models showed that model 2 (participant random), which accounts for individual differences in pain intensity ratings, was the best model fit when intensities 3, 6 and 7 were delivered. When intensities 4 and 5 were delivered, model 3 (participant-cue random), which accounts for individual differences in how cue is incorporated into pain perception, was the best model. Statistical results can be found in Table 4.5.

Table 4.5: Statistical summary of confirmation of the cue effect. Effects of fixed terms (i.e. parametric terms) and smooth terms are shown, with their corresponding statistical values. For trials where delivered intensities were 3, 6 and 7, the best model fit was the one that accounted for individual differences in pain perception. For trials where delivered intensities were 4 and 5, the best model fit was one which accounts for individual differences in how cue is incorporated into pain perception. Cues were found to have significant fixed effects for all intensities. With the exception of delivered intensity 3, an effect of trial was also found. * $p < .05$, ** $p < .01$, *** $p < .001$

Delivered intensity	Best model	Parametric terms			Smooth terms			Adjusted R^2	AIC
		Term	estimate	p-value	Term	edf	p-value		
3	2 (participant random)	Cue	0.437	< .001***	Trial	0.560	.186	.419	2165.60
		Autism vs. Non-autism	-0.146	.486	Subject	63.60	< .001***		
		Alexithymia vs. Non-alexithymia	0.102	.629					
4	3 (participant-cue random)	Cue	0.586	.001**	Trial	1.949	< .001***	.508	2321.93
		Autism vs. Non-autism	-0.163	.393	Subject, cue	121.52	< .001***		
		Alexithymia vs. Non-alexithymia	0.220	.253					
5	3 (participant-cue random)	Cue	0.723	< .001***	Trial	1.04	< .001***	.578	2374.73
		Autism vs. Non-autism	-0.241	.272	Subject, cue	126.95	< .001***		
		Alexithymia vs. Non-alexithymia	0.105	.635					
6	2 (participant random)	Cue	0.833	< .001***	Trial	0.975	< .001***	.476	2566.60
		Autism vs. Non-autism	-0.233	.410	Subject	64.53	< .001***		
		Alexithymia vs. Non-alexithymia	0.301	.291					
7	2 (participant random)	Cue	0.938	< .001***	Trial	0.979	< .001***	.467	2533.58
		Autism vs. Non-autism	-0.206	.445	Subject	63.77	< .001***		
		Alexithymia vs. Non-alexithymia	0.265	.329					

GAM-cue analysis (Figure 4.5) showed an effect of cue, confirming that participants incorporated expectations signaled by the cue into their pain perception. The best fit GAM-cue models (per intensity level) explained between 41.9% and 57.8% of the variance in pain ratings. With the exception of when level 3 intensity was delivered, there was an effect of trial, whereby pain intensity rating decreased across trials, suggestive of habituation. And finally, across all intensities, no effect of autism group nor alexithymia group were found. These results confirmed the presence of the cue effect, and therefore it made sense to continue the analyses exploring the effect of prediction error on pain perception.

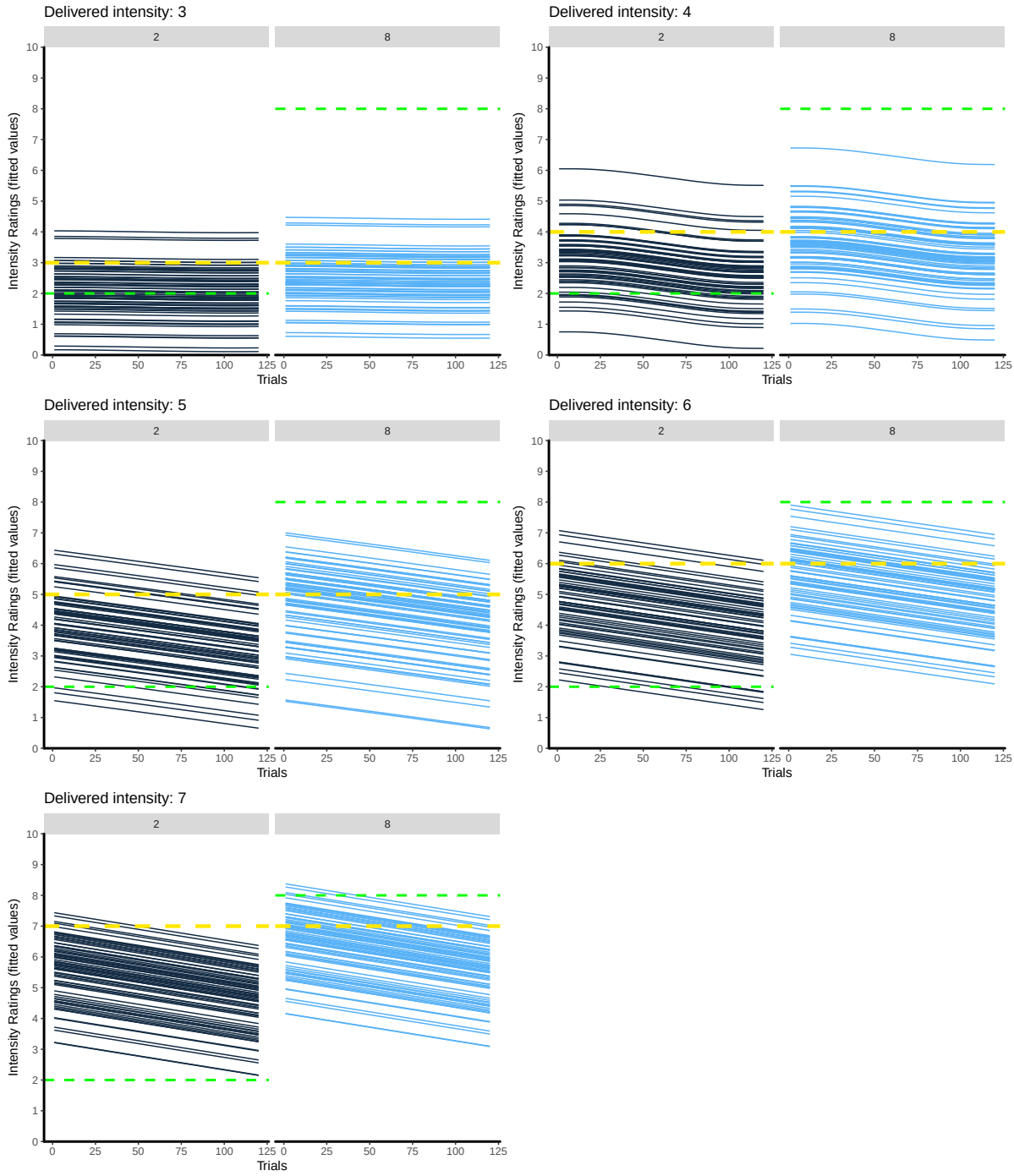


Figure 4.5: Confirmation of the cue effect. Fitted pain ratings are shown across trials (1-120) for two non-veridical cues (2 and 8) for trials where the prediction error was greater than 0 (delivered stimulus intensity: 3 through 7). The dashed yellow lines indicate the delivered stimulation intensity, and dashed green lines indicate the value of the cue. There was an effect of cue, where participants viewed pain stimulations following different cues (2 and 8) differently, despite receiving the same stimulation intensity. There was also an effect of trial, except when pain level 3 was delivered.

Effects of prediction error size

After confirming the presence of the cue effect across all trials where prediction error was not 0, the next step in the analysis was to check whether the cue effect differed depending on the size of the prediction error. While the tipping point theory covers both positively and negatively valenced prediction error, it was first necessary to determine whether there was an effect of size, before moving on to assessing the effect of valence. To do this, positively and negatively valenced prediction errors were collapsed to the absolute value of the prediction error, as the prediction error size, not valence, was of the interest in this particular analysis. The absolute value of subjective error was used as the dependent variable, as again, the magnitude of the cue effect (i.e., subjective error), not valence, was of interest in this analysis.

Three GAM-pe_size models were compared, and model 2 (participant random), which accounts for individual differences in absolute subjective error, was the best model fit [AIC = 13370.11, adjusted R^2 = .283]. Statistical results are summarised in Table 4.6. The relationship between subjective error and prediction error, as illustrated in Figure 4.6, approximated a quadratic curve [edf = 2.31, $p < .001$]. This is consistent with the tipping point theory, as the relationship is best described as an inverted U-shaped curve whereby subjective error increases as prediction error increases until a point, but then starts to fall. No effect of autism nor alexithymia were observed. Results therefore suggest that the magnitude of the prediction error, irrespective of the valence (as absolute scores were used), was a significant predictor of the subjective error size.

Effects of prediction error valence

Given the findings that prediction error size is an important factor for subjective error, further GAM analyses were conducted to assess whether the valence of prediction error was also important. To assess the effect of prediction error valence, absolute values of subjective error were used for this particular analysis.

Overall effect of prediction error valence First, GAM-pe_valence:overall model was performed, which modelled across all levels of prediction error (signed, not absolute), with a smooth

term of prediction error (signed, not absolute). Comparison of three GAM-pe_valence:overall models revealed that model 2 (participant random), which accounts for individual differences in subjective error, was the best model fit [AIC = 13052.34, adjusted R^2 = .333]. GAM-pe_valence:overall analysis showed an effect of prediction error and trial, and explained 33.3% of the variance in the absolute value of subjective error. Statistical results are summarised in Table 4.6. GAM-pe_valence:overall, again, similar to GAM-pe_size model, revealed a relationship between subjective error and prediction error that is consistent with the tipping point theory [edf = 6.40, $p < .001$], whereby subjective error increased as prediction error increased, until a tipping point (later for positive prediction errors than negative prediction errors) where subjective errors started to decrease. No significant effects of autism group and alexithymia group were found. The relationship is illustrated in Figure 4.6.

Table 4.6: Statistical summary of effect of the prediction error size and valence. Effects of fixed terms (i.e. parametric terms) and smooth terms are shown, with their corresponding statistical values. The size (absolute magnitude) and valence of prediction error were found to have significant effects, along with trial. No effect of autism nor alexithymia groups were found. abs: absolute value. * $p < .05$, ** $p < .01$, *** $p < .001$

	Parametric terms			Smooth terms			Adjusted R^2	AIC
	Term	estimate	p-value	Term	edf	p-value		
Absolute magnitude	Autism vs. Non-autism	0.167	.291	Prediction error (abs)	2.31	< .001***	.283	13370.11
	Alexithymia vs. Non-alexithymia	-0.195	.221	Trial	0.991	< .001***		
				Subject	69.79	< .001***		
Valence	Autism vs. Non-autism	0.167	.289	Prediction error	6.40	< .001***	.333	13052.34
	Alexithymia vs. Non-alexithymia	-0.194	.222	Trial	0.996	< .001***		
				Subject	70.01	< .001***		

Effect of valence at varying levels of prediction error size Given the finding that prediction error size and valence are significant predictors of subjective error, further analysis was conducted to assess whether there were differences in the effect of valence at varying levels of prediction error size. GAM-pe_valence:individual models were performed per each level of prediction error size (i.e, ±1 to ±6) with prediction error as a factor term (positive and negative). Three GAM-pe_valence:individual models were performed per prediction error size, resulting in a total of 18 models. Comparison between the three GAMs showed that model 2 (participant random), which accounts for individual differences in subjective error, was the best model fit for all magnitudes of prediction error. Statistical results are summarised in Table 4.7.

The relationship between absolute subjective error and trial as a function of valence at each

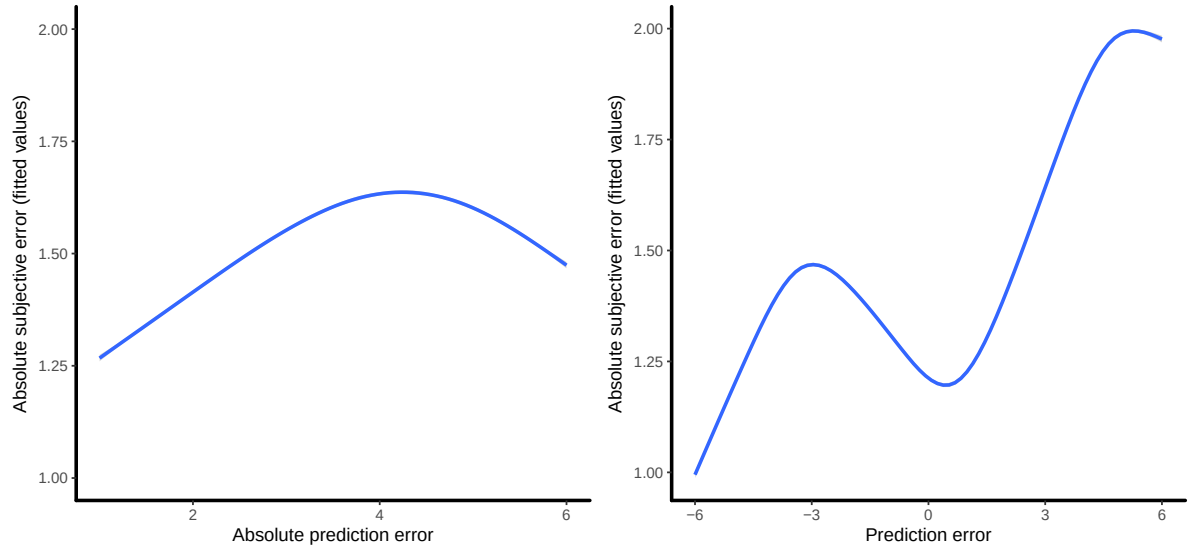


Figure 4.6: Effect of prediction error size and valence. Fitted values of absolute value of subjective error per (left) absolute value of prediction error, and (right) full range of prediction error are shown. Subjective error of 0 indicates that delivered and rated stimulus levels were the same (i.e., perfect perception of sensory evidence). In both analyses, there was an effect of prediction error and trial, but no autism nor alexithymia group effects were found. The results are suggestive of the tipping point theory, whereby the subjective error starts to decrease as the prediction error becomes larger, but with less of an effect for placebo conditions (i.e., prediction error is positive, as the delivered stimuli is more painful than expected).

Table 4.7: Statistical summary of the effect of valence at varying prediction error size. Effects of fixed terms (i.e. parametric terms) and smooth terms are shown, with their corresponding statistical values. The estimates for prediction error are for positive prediction errors. For all valence of prediction error, the effect of prediction error was significant, but no effect of autism group was found. For prediction error ±6, an effect of alexithymia group was found. * $p < .05$, ** $p < .01$, *** $p < .001$.

			Prediction error					
	Terms	Statistics	±1	±2	±3	±4	±5	±6
Parametric Terms	Prediction error	estimate	-0.118	$-4.24\text{x}10^{-3}$	0.175	0.451	0.827	0.982
		p-value	.114	.951	.006**	< .001***	< .001***	< .001***
	Autism vs. Non-autism	estimate	$5.35\text{x}10^{-2}$	$6.38\text{x}10^{-2}$	0.203	0.213	0.247	0.215
		p-value	.732	.725	.305	.242	.166	.211
	Alexithymia vs. Non-alexithymia	estimate	$-6.61\text{x}10^{-2}$	-0.134	-0.225	-0.193	-0.207	-0.342
		p-value	.674	.464	.261	.293	.250	.048*
Smooth Terms	Trial	edf	1.38	0.936	0.929	1.65	1.85	0.905
		p-value	.004**	< .001***	< .001***	< .001***	< .001***	.001**
	Subject	edf	54.97	61.32	64.82	60.87	57.343	54.20
		p-value	< .001***	< .001***	< .001***	< .001***	< .001***	< .001***
Model Fit	Adjusted R^2		0.237	0.348	0.451	0.367	0.352	0.337
	AIC		2214.40	2126.53	1989.68	2158.80	2293.95	2359.00

size of prediction error can be found in Figure 4.7. GAM-pe_valence:individual models showed an effect of prediction error valence and trial when the prediction error was between ±3 and ±6. The models explained between 23.7% and 45.1% of the variance. This result replicates Hird et al.'s (2019) finding that there were differences in the effect of prediction error depending on its valence. The current findings show that the magnitude of subjective error becomes bigger

in placebo conditions (positive valence) than in nocebo conditions (negative valence) as the magnitude of the prediction error increases.

There is a general trend of a linear relationship between subjective error and trial [$0.929 \leq$ edf ≤ 1.85, $.0001 \leq p \leq .004$], whereby the subjective error increases as participants undergo more trials. This trend shows that the effect of the cue increases as participants complete trials. The trial type of most interest is those with prediction error of ±3, as no matter the cue (2 or 8), the delivered stimulation level is 5. As with the other degrees of prediction error, subjective error is significantly smaller when the prediction error is positive than when it is negative [estimate = 0.175, p = .006].

No effect of autism group was observed in any size of prediction error. However, at the extreme of the prediction error size (±6) the alexithymia group had a bigger subjective error than the non-alexithymia group [estimate = -0.342, p = .048].

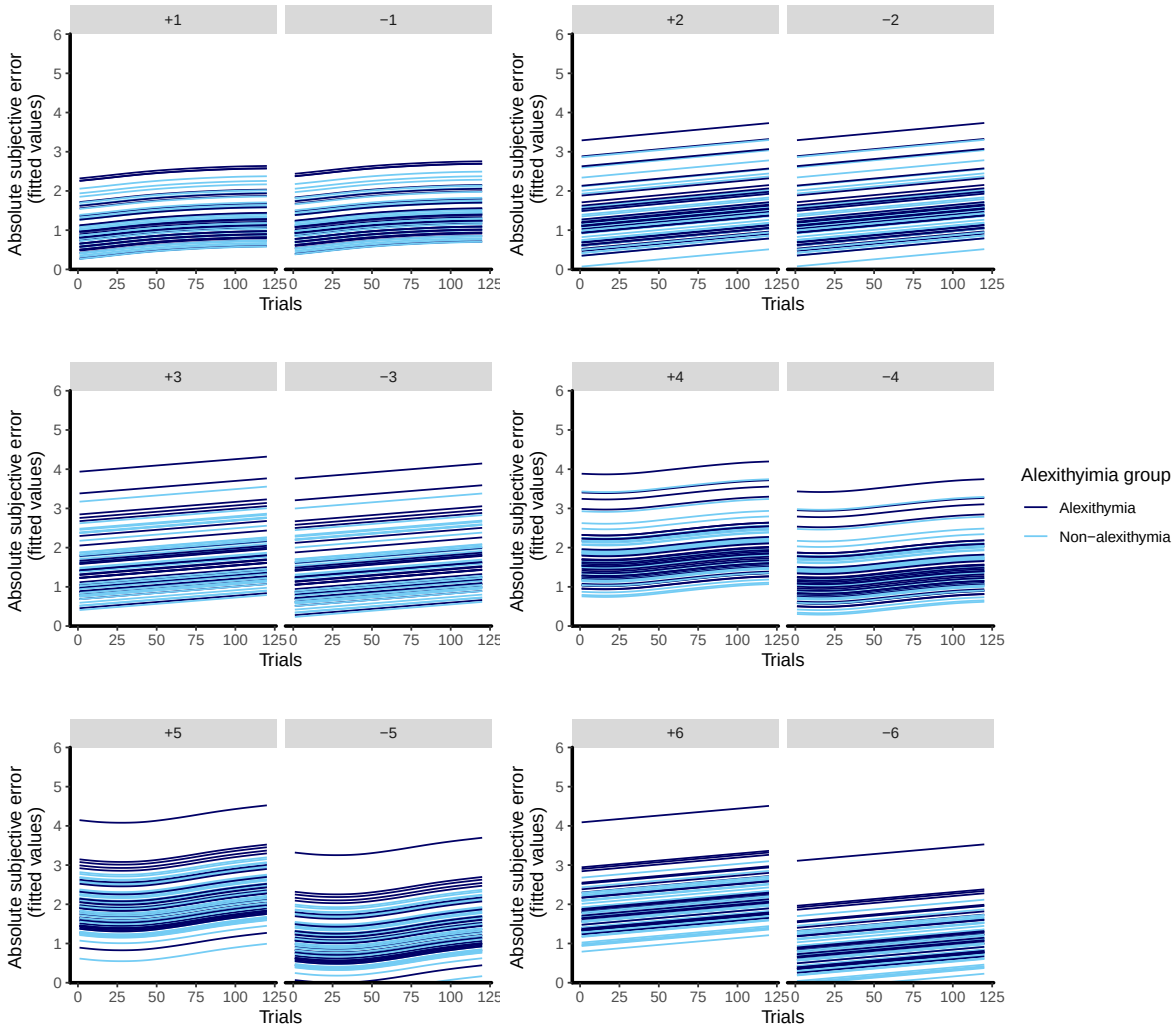


Figure 4.7: Effect of valence per each level of prediction error. Fitted values of absolute subjective errors are shown across trials by the magnitude of prediction errors. Subjective error of 0 indicates that delivered and rated stimulus levels were the same. Each line represents a participant: dark purple indicates those in alexithymia group, and light blue lines are those in non-alexithymia group. The numbers in grey boxes indicate the magnitude of prediction errors. Ones with positive prediction errors are where participants saw cue 2, and therefore the delivered stimulation was more painful than the cued intensity. Negative prediction errors indicate where participants saw cue 8, and so received stimulation levels that were less painful than the cued intensity. There was an effect of the valence for prediction error ±3 through ±6, as well as an effect of trial for all prediction error sizes. For ±6, there was also an effect of alexithymia group, but no autism group effect was observed.

4.3.3 Relationship Between Prediction Error and Subjective Error

Replication of Hird et al.'s (2019) analysis

In Hird et al.'s (2019) analysis, several variables in addition to prediction error and subjective error were included so that they are accounted for. By conducting the GAM analyses presented above, it was confirmed that the addition of the extra variables in Hird et al.'s (2019) NLME analysis strategy was also appropriate for the present study. These were as follows.

First, it was deemed suitable to conduct NLME analyses, which aimed to determine the relationship between subjective error and prediction error, as there was an effect of cue (see Section 4.3.2). Second, the addition of the term of trial was also justified as a significant habituation effect was observed (see Section 4.3.2). Third, the addition of fourth order quartic term of prediction error (PE^4) was deemed appropriate, as an effect of prediction error size (see Section 4.3.2) and valence (see Section 4.3.2) on subjective error were found. And finally, a random intercept of participant was deemed necessary as the best model fit for all of GAM analyses had a random effect of participants. For these reasons, similar to Hird et al.'s (2019) analysis, the polynomial prediction error terms and their interaction with trial (i.e., trial $\times$ PE, trial $\times$ PE^2, trial $\times$ PE^3, trial $\times$ PE^4) were added, along with a random intercept of participant.

Results of the final model can be found in Table 4.8. Unlike Hird et al.'s (2019) results, the addition of random slopes in the polynomial terms of prediction error (PE, PE^2, PE^3 and PE^4) and random intercept of participant improved the models significantly. The results suggest that the quartic term in PE, trial, and some interactions betwen PE and trial are needed to explain the relationship between prediction error and subjective error. The main effects and interaction terms of prediction error and trial were significant, but any terms including the quadratic term of prediction error (PE^2) were not significant (i.e., PE^2, PE^2 $\times$ trial).

As shown in Figure 4.8, there were differences in the polynomial relationships between prediction error and subjective error per block. Unlike Hird et al.'s (2019) findings, where they found the quartic relationship become more linear as the trials went on, in the present data, the relationship was more quartic in the last block compared to the first block, indicating that the relationship between prediction error and subjective error changed through the course of

the task. Furthermore, given the alexithymia group effect on the prediction error valence on subjective error (see Section 4.3.2), further analysis assessing the influence of AQ-50 and TAS-20 on the polynomial relationship between prediction error and subjective error was performed. An illustration of the relationship between subjective error and prediction error per participant can be found in Section A.3.2.

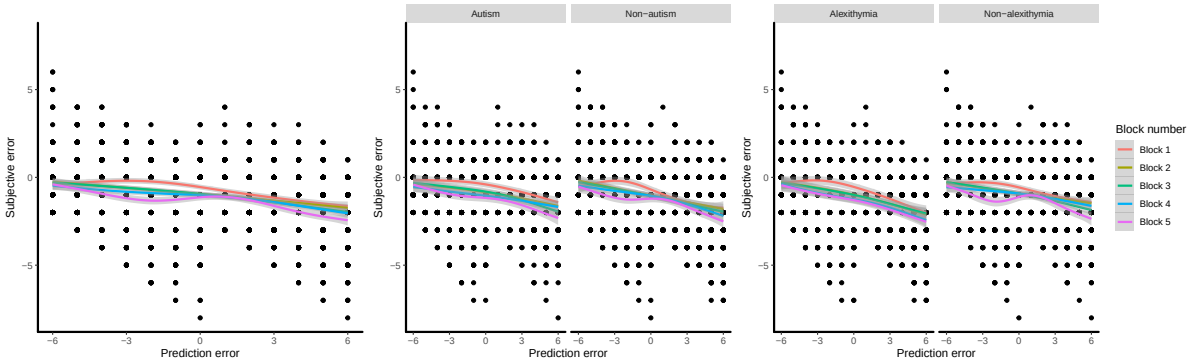


Figure 4.8: Polynomial relationship between prediction error and subjective error. The relationship between prediction error and subjective error are shown per block (1 through 5) for (left) all participants, (middle) autistic and non-autistic participants, and (right) alexithymic and non-alexithymic participants. Each dot represents a trial from single participants, though there are significant overlaps between participants. In non-clinical participants (non-autism and non-alexithymia groups), there is a general trend of the relationship becoming more quartic as the trials go on, whereas the opposite trend is seen for clinical participants (autism and alexithymia groups), where the relationship becomes more linear in later blocks compared to earlier blocks.

Effect of autistic and alexithymic traits

To investigate the effect of autistic and alexithymic traits on the relationship between prediction error and subjective error, the same NLME model was run with interaction terms of autistic traits and alexithymic traits, which were both z-scored. Interaction terms were added separately, due to the high correlation between AQ-50 and TAS-20. The model excluding any terms with quadratic term of prediction error (i.e., PE^2, $PE^2 \times$ trial, $PE^2 \times$ AQ-50, $PE^2 \times$ trial $\times$ AQ-50, $PE^2 \times$ TAS-20, $PE^2 \times$ trial $\times$ TAS-20) was the best performing model, with random slopes in the polynomial terms of prediction error (PE, PE^2, PE^3 and PE^4) and random intercept of participant. Results of the final model can be found in Table 4.8.

Table 4.8: Results of the NLME models fitted for (left) Hird et al. (2019) replication and (right) NLME model including autistic and alexithymic traits. Predictor: the predictor variable entered into the model; $\hat{\beta}$: the estimated beta coefficient; SE: standard error of $\hat{\beta}$; p-value: indicates whether a predictor variable significantly predicts the data or not. * $p < .05$, ** $p < .01$, *** $p < .001$.

Predictor	NLME replication			NLME with autistic and alexithymic traits		
	$\hat{\beta}$	SE	p-value	$\hat{\beta}$	SE	p-value
Intercept	-0.598	9.89×10^{-2}	.000***	-0.475	8.94×10^{-2}	.000***
Trial	-5.02×10^{-3}	8.26×10^{-4}	.000***	-5.97×10^{-3}	6.09×10^{-4}	.000***
PE	-0.202	2.75×10^{-2}	.000***	-0.205	2.68×10^{-2}	.000***
PE^2	-4.85×10^{-3}	1.11×10^{-2}	.661			
PE^3	2.95×10^{-3}	1.07×10^{-3}	.006**	3.10×10^{-3}	1.06×10^{-3}	.004**
PE^4	-1.54×10^{-4}	3.21×10^{-4}	.632	-3.32×10^{-4}	7.67×10^{-5}	.000***
AQ-50				0.152	0.105	.153
TAS-20				2.17×10^{-2}	0.106	.838
Trial × PE	1.59×10^{-3}	3.26×10^{-4}	.000***	1.60×10^{-3}	3.26×10^{-4}	.000***
Trial × PE^2	-2.28×10^{-4}	1.32×10^{-4}	.084			
Trial × PE^3	-6.46×10^{-5}	1.21×10^{-5}	.000***	-6.49×10^{-5}	1.20×10^{-5}	.000***
Trial × PE^4	7.90×10^{-6}	3.69×10^{-6}	.033*	1.70×10^{-6}	1.03×10^{-6}	.091
Trial × AQ-50				-1.75×10^{-3}	7.17×10^{-4}	.014*
Trial × TAS-20				2.34×10^{-4}	7.15×10^{-4}	.744
PE × AQ-50				6.70×10^{-2}	3.16×10^{-2}	.034*
PE^3 × AQ-50				-9.96×10^{-4}	1.24×10^{-3}	.424
PE^4 × AQ-50				-6.82×10^{-5}	8.97×10^{-5}	.447
PE × TAS-20				-5.56×10^{-2}	3.14×10^{-2}	.077
PE^3 × TAS-20				6.66×10^{-4}	1.24×10^{-3}	.590
PE^4 × TAS-20				-2.40×10^{-4}	8.95×10^{-5}	.008**
Trial × PE × AQ-50				-2.56×10^{-4}	3.83×10^{-4}	.504
Trial × PE^3 × AQ-50				-3.70×10^{-6}	1.41×10^{-5}	.792
Trial × PE^4 × AQ-50				1.10×10^{-6}	1.20×10^{-6}	.375
Trial × PE × TAS-20				-1.46×10^{-4}	3.83×10^{-4}	.702
Trial × PE^3 × TAS-20				1.60×10^{-5}	1.41×10^{-5}	.256
Trial × PE^4 × TAS-20				2.40×10^{-6}	1.19×10^{-6}	.042*
AIC	17147.89			17355.76		
BIC	17325.05			17624.67		
Log-likelihood	-8546.95			-8636.88		

The results continue to show significant main effects and interaction terms of prediction error and trial, with the exception of trial × PE^4 interaction term. This is similar to Hird et al.'s (2019) findings, where they found discordant results between their two datasets for trial × PE^3 and trial × PE^4 interaction terms, suggesting that these two terms may be more sensitive to individual differences and other nuisance variables. For terms including autistic or alexithymic traits, interaction terms of i) AQ-50 × trial, ii) AQ-50 × PE, iii) TAS-20 × PE^4, and iv) TAS-20 × trial × PE^4 were found to be significant (see Figure 4.9). The results suggest that while the effect of prediction error seems to be modulated by both autistic and alexithymic traits, autistic traits only seem to significantly modulate the interaction with non-polynomial prediction error (i.e., AQ-50 × PE), but not how that relationship changes across trials.

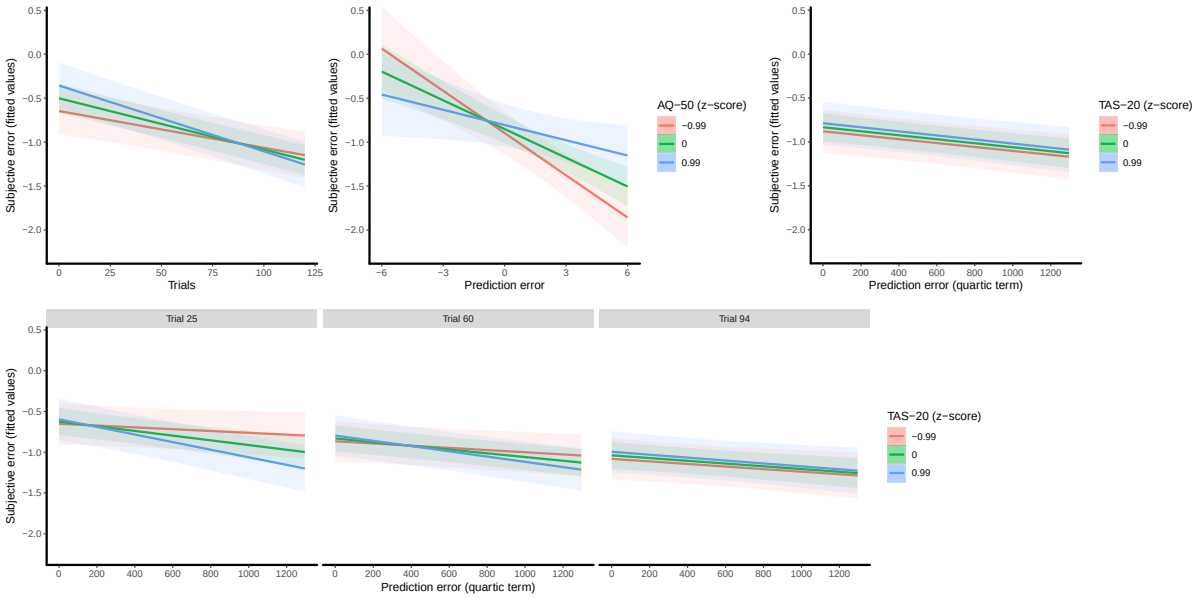


Figure 4.9: Relationships between relevant NLME terms and fitted values of subjective error. Top: Fitted values of subjective error against (left) autistic trait and trial interaction (AQ-50 × trial), (middle) autistic trait and prediction error interaction (AQ-50 × PE), (right) alexithymic traits and quartic term of prediction error interaction (TAS-20 × PE^4), bottom: fitted values of subjective error against alexithymic trait, quartic term of prediction error, and trial interaction (TAS-20 × trial × PE^4). Autistic and alexithymic scores are grouped into three categories according to the z-scores: -0.99 indicates those with lower than the mean score, 0 indicates those with mean scores, and 0.99 indicates those with higher than the mean score. Trial is also broken into three parts for illustrative purposes. Shaded regions indicate the 95% confidence interval.

Interestingly, the quartic relationship between prediction error and subjective error (the pattern indicating a tipping point) seems to be affected by alexithymic traits, but not by autistic traits. The more alexithymic one is, the more quartic the relationship between prediction error and subjective error is. There is also an interaction with trial, whereby the prediction error and

subjective error relationship becomes less quartic as the trials go on, as shown in Figure 4.9.

Effect of other self-report measures

In the present study, other related self-report measures were collected to control for relevant but often highly correlated measures. To take these nuisance covariates into account, elastic net regression was performed.

Simple correlations Simple correlations of all self-report measures that were used as independent variables in the elastic net analysis can be found in Table 4.9. As expected, many of the self-report questionnaire scores were highly correlated with one another. Age, however, was not correlated with any of the self-report questionnaire measures. For random slope of polynomial prediction error terms from the NLME analysis, the only significant correlation was found between PE term (first order prediction error) and pain catastrophising trait (PCS).

Table 4.9: Simple correlations between self-report measures and prediction error variables. AQ-50: autistic traits, TAS-20: alexithymic traits, STAI-1: state anxiety, STAI-2: trait anxiety, BDI-II: depressive traits, PCS: pain catastrophising trait, BPQs-A: bodily awareness, IAS: interoceptive accuracy, IATS: interoceptive attention, IUS-12: intolerance of uncertainty, FSIQ: cognitive intelligence, and random slope terms of polynomial terms of prediction error. * $p < .05$, ** $p < .01$, *** $p < .001$.

														Random slope		
		Age	AQ-50	TAS-20	STAI-1	STAI-2	BDI-II	PCS	BPQs-A	IAS	IATS	IUS-12	FSIQ	PE	PE^2	PE^3
	Age															
	AQ-50	.302														
	TAS-20	-.063	.795***													
	STAI-1	-.258	.614*	.678**												
	STAI-2	-.319	.613*	.836***	.852***											
	BDI-II	-.222	.690**	.779***	.819***	.931***										
	PCS	.070	.639**	.743***	.700**	.763***	.747***									
	BPQs-A	.229	-.045	-.109	.197	.166	.176	.271								
	IAS	.102	-.803***	-.832***	-.704**	-.675**	-.652**	-.605*	.115							
	IATS	.174	.242	.135	.501*	.377	.457	.609*	.586*	-.049						
	IUS-12	.040	.731**	.791***	.708**	.810***	.818***	.849***	.156	-.612*	.554*					
	FSIQ	-.388	-.133	-.027	-.001	-.085	-.261	-.441	-.399	-.166	-.598*	-.466				
	PE	.132	-.114	-.421	-.371	-.405	-.233	-.520*	.036	.232	-.250	-.349	-.005			
Random	PE^2	.038	.169	.072	.234	.094	.035	.082	-.083	-.218	.137	-.005	.241	-.279		
slope	PE^3	-.242	.071	.341	.342	.315	.138	.375	-.157	-.279	.099	.237	.134	-.943***	.294	
	PE^4	-.022	-.178	-.111	-.267	-.133	-.059	-.130	.080	.235	-.161	-.032	-.234	.357	-.997***	-.366

Elastic net Results of the elastic net regression models can be found in Table 4.10. All variables were centred prior to analysis.

First, an elastic net model was run with subjective error as the dependent variable, and self-report questionnaire measures, and polynomial terms of prediction error as independent variables (model 1 in Table 4.10). This was done to confirm GAM and NLME results. Subjective

Table 4.10: Results of the elastic net models with nuisance covariates. Dependent variable: the dependent variable entered into the model; λ: the largest λ at which the MSE is within 1 standard error of the smallest MSE; Measure: the loss used for cross-validation; SE: standard error; Non-zero: number, name and the corresponding coefficient of non-zero coefficients. A constant of 1000 was added to all variables prior to log transformation, followed by centring.

Model	Dependent variable	λ	Measure	SE	Non-zero variables		
					N	Name	Coefficients
1	Subjective error (average)	0.130	0.862	5.15×10^{-2}	1	PE	-0.364
2a	PE slope	0.303	1.02	0.134	0		
2b	PE^2 slope	0.125	1.03	0.157	0		
2c	PE^3 slope	0.175	1.04	0.137	0		
2d	PE^4 slope	0.130	1.03	0.147	0		

error was averaged per prediction error per participant, as the present was a repeated-measures experiment. This model excludes the effect of trial, as the dependent variable is averaged out across the entire duration of the task. Only the first order polynomial prediction error (PE) was found to be a non-zero coefficient, suggesting that all self-report measures are non-significant predictors.

Second, elastic net models with random slope coefficients from the NLME model from the replication of Hird et al.'s (2019) analysis strategy (see Section 4.3.3) were run (models 2a through 2d in Table 4.10). None of the models had any non-zero coefficients, suggesting that none of the nuisance covariates that were collected for the present study, including autistic and alexithymic traits, were significant predictors for the random slopes of polynomial prediction error terms.

4.4 Discussion

The present study investigated whether expectation modulates perception differently depending on the magnitude and the valence of the prediction error in accordance with the "tipping point" theory (Hird et al., 2019), and whether the tipping point is modulated by autistic (Pellicano & Burr, 2012) or alexithymic traits (Brewer et al., 2015).

First, GAM analyses were conducted to assess the assumptions made in Hird et al.'s (2019) NLME analysis strategy. These were the presence of a habituation effect, cue effect, effect

of prediction error size, and valence. Across all delivered stimulation intensity levels, the perceived pain on non-veridical cue trials depended on whether participants viewed cue 2 or 8 – thus demonstrating that expectation of the degree of upcoming pain influenced pain perception. Analyses showed that the prediction error valence and size (whether the stimulation was more or less painful than expected, and by how much) had an effect on the magnitude of subjective error. The effect of valence was asymmetric: placebo conditions (when perceived pain was greater than that expected; cue 2) had greater subjective errors than nocebo conditions (when perceived pain was less than expected, cue 8). Additionally, an alexithymia effect, but no autism effect, was found for the largest prediction error (±6), whereby the more alexithymic one was, the larger the subjective error.

The NLME analysis showed evidence of the tipping point – that the influence of expectations on perception decreases after the magnitude of the prediction error crosses a crucial point – and that the size of this effect is modulated by autistic and alexithymic traits, but how it develops over trials is modulated by alexithymic traits. The higher the autistic traits, the less pronounced the effect of cue, meaning that those with high autistic traits were less influenced by the expectation, supporting the Bayesian account of autism (Pellicano & Burr, 2012). For alexithymic traits, the higher the alexithymic traits, the greater the tipping point (the quartic relationship between prediction error and subjective error) early on in the task, but the less pronounced the tipping point becomes later in the task. This suggests that the tipping point effect weakens for alexithymic participants as they undergo further conditioning. These results suggest that while autistic traits modulate how expectation influences pain perception, atypical perceptual learning in pain may be driven by alexithymic traits.

Prediction error is key to learning, for without prediction error, learning is not possible (Den Ouden et al., 2012; Keiflin & Janak, 2017). Our findings suggest that due to the significant interaction with trials, learning in the context of interoceptive perception may be modulated by alexithymic traits, not autistic traits. This follows the results from Chapter 3, whereby the extinction function (i.e., how prediction error is incorporated to update priors and influence perception) was most complex for the aut+alex group compared to all other groups. The difference in learning modulated by alexithymic traits may be one of the reasons why there are

conflicting results in studies investigating the Bayesian account of autism (Goris et al., 2018; Lawson et al., 2017; Tewolde et al., 2018). Further, a recent paper by Hird et al. (2023) found that the value of the cue changed throughout the course of the task, demonstrating the occurrence of learning.

However, the above mentioned results should be interpreted with caution, as the elastic net models including nuisance covariates did not find an effect of either autism or alexithymia (though the non-significant results may be due to lack of power). Thus, it is possible that the apparent alexithymia effect is due to its covariance with another trait, but it is also possible that inclusion of additional traits (e.g., the pain catastrophising) resulted in insufficient unique variance to observe an effect of alexithymia. Regardless, GAM and NLME models showed substantial effects of individual differences in pain experience, in line with previous literature (Hoskin et al., 2019).

One limitation of the study related to the nature of the numerical pain scale should be noted (Figure 4.10). Although an effect of prediction error valence was found, the results should be considered with caution. This is because having the same prediction error size (in cues 2 and 8) is not equivalent to having the same range of subjective errors.

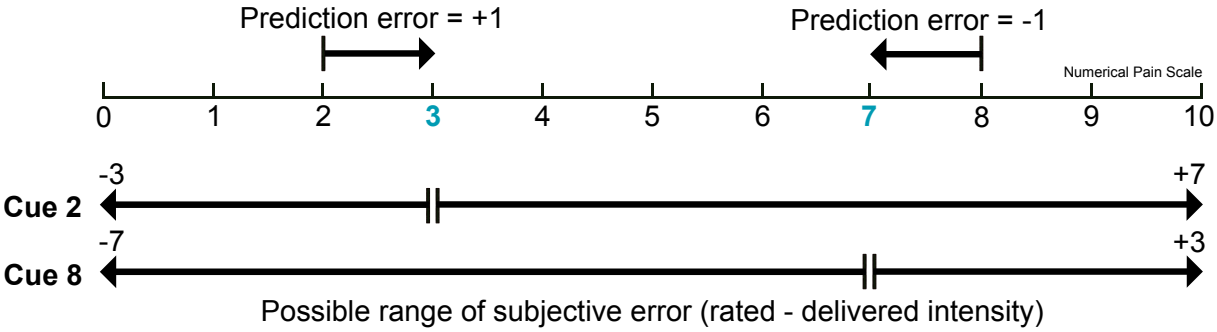


Figure 4.10: Limitation related to the nature of the numerical pain scale. An example where prediction error is ± 1 is shown. The number marked in blue on the scale is the intensity of the delivered pain stimulus (cue 2: level 3, cue 8: level 7). The range of subjective error for (top) cue 2, and (bottom) cue 8 are shown below the numerical pain scale. For cue 2, subjective error ranges from -3 to +7, whereas for cue 8, subjective error ranges from -7 to +3.

For example, as illustrated in Figure 4.10, for prediction error of +1 (i.e., when cue 2 is presented but level 3 pain is delivered), subjective error can only range from -3 to +7, rather than the full range of ± 7 (subjective error could only be ± 8 if the prediction error was 0). As in, due to the pain rating scale ranging from 0 to 10, the lowest possible rating was 0 (subjective error:

-3), and the highest possible rating was 10 (subjective error: +7). Whereas for prediction error of -1 (i.e., when cue 8 is shown by level 7 pain is delivered), subjective error could range from -7 to +3. In the analysis assessing the effect of valence of prediction error, the absolute value of the subjective error was used to circumvent this issue, to ensure that the range of prediction error was the same for each cue types (i.e., in the example given above, the range would be 0 through 7 for both cue 2 and 8). The asymmetric nature of the subjective error range depending on the cue likely explains the asymmetric effect of prediction error valence (i.e., the influence of the quartic term of the prediction error). This valence-dependent sensitivity makes it harder to observe a quartic curve relationship between prediction error and subjective error, but it would not artefactually produce it, nor would it produce an interaction with autism and alexithymia. Moreover, the GAM analysis showed significant effect of prediction error valence at ±5, where the subjective error ranged between -5 and +5 for both cue 2 and 8, suggesting that the findings are not an artefact of this feature of the design. It is therefore a limitation that reduces the sensitivity of the design, but does not account for the presence of significant quartic relationship (and its interaction with alexithymic traits) found in the present study.

A further feature of note was that the calibration process for alexithymic participants was especially difficult, when compared to the neurotypical participants. The calibration process requires participants to re-identify the stimulation levels that they previously rated, to ensure that the calibrated pain levels are appropriate. Often alexithymic participants were initially anxious about the process which may have heightened their pain perception (Failla, Gerdes, et al., 2020), and then this quickly dissipated as the calibration process continued. A careful calibration was therefore required to ensure that appropriate pain levels were being used. The calibration process for alexithymic participants took longer than others, as they had additional difficulties discriminating pain levels. Anecdotally, it seemed that there may be differences in pain granularity between alexithymic and non-alexithymic participants. Future studies may gain insight into this process by repeating the study using physiological and EEG measures, focusing on features such as GSR and mismatch negativity to assess whether there are similarities or discrepancies between behavioural and non-behavioural measures.

This study replicated the findings by Hird et al. (2019), and showed that there does exist a

tipping point. While autistic traits influence the effect of the cue on pain perception, alexithymic traits influence the tipping point and how it changes over the course of the task. This finding, similar to Chapter 3, supports the alexithymia hypothesis in autism in the interoceptive domain, specifically, in pain perception. The results suggest that it is alexithymic traits, not autistic traits, that shape the formation of how prediction error size and valence affect one's pain perception.

Chapter 5

Effects of probabilistic expectations on interoceptive and exteroceptive perception

Abstract

Cues that elicit expectations about upcoming stimulus can be deterministic (100% predictive probability) or probabilistic. While earlier studies in this thesis assessed the effect of autism and alexithymia on the effect of deterministic cues on perception, this chapter reports work examining their effect on probabilistic cues. Drift diffusion model (DDM) was used to model the impact of probabilistic cues on perception, which enables the impact of cues on different processing stages of perception to be established. While autistic perception has been studied previously with DDM before, no study has used DDM in the context of pain perception in autism. The present study used a probabilistic cueing paradigm where participants were presented with two cues, each with different probabilistic outcomes of high and low stimuli. Two studies were conducted. One study used pain stimuli (an interoceptive signal; Study 1), and the second used visual stimuli (an exteroceptive signal; Study 2). The results showed no effects of autism or alexithymia, however, an effect of intolerance of uncertainty was found for the study using pain stimuli (Study 1). Further research with tasks that have greater difficulty are needed to minimise the ceiling effect in task performance, and thereby increase the magnitude of the cue effect. This will allow to determine the impact of autism or alexithymia on the variables identified using

DDM.

5.1 Introduction

Expectations about upcoming pain are often presented in the form of visual cues in experimental paradigms (Au Yeung et al., 2014; Hird et al., 2019; Hoskin et al., 2019). In Chapters 3 and 4, cues were deterministic: the value of cues (at least as conveyed to the participant) had a 100% predictive probability. However, cues can be probabilistic, such that a cue provides the likelihood of a range of outcomes to participants, meaning some outcomes are more (un)predictable than others (i.e., the precision of priors is more variable). In the context of pain, introducing uncertainty in expectations affects pain intensity ratings (Zaman et al., 2021), and probabilistic cues, when compared to deterministic cues, lead to increased pain intensity ratings (Brown et al., 2008; Lin et al., 2014). Further, the uncertainty of cues has been shown to result in higher pain ratings (Yoshida et al., 2013), although Zaman et al. (2017) found that ratings were unaffected by uncertainty.

Of most interest are the results of a study by Wiech et al. (2014) who compared the effects of two cues with different probabilistic outcomes on pain perception using a drift diffusion model (DDM), a computational model that allows to separate the changes in sensory processing and decision-making due to the cue effect (Wiech et al., 2014). DDM (see Figure 5.1 for a schematic illustration) is a sequential sampling model that assumes individuals continuously collect noisy information about two possible outcomes (e.g., the level of pain in a two-alternative forced choice (2AFC) task) until the evidence meets the threshold to make a decision about one outcome or another (Forstmann et al., 2016; Ratcliff, 1978).

DDM separates the different processing stages involved in decision-making, which allows for a more nuanced understanding of the differences in task performance. This is a more sensitive measure compared to conventional measures, such as task accuracy and reaction time. DDM has three key parameters, boundary separation, starting point, and drift rate. It also allows calculation of non-decision time. Boundary separation (α) refers to the distance between lower and upper decision thresholds and is indicative of response caution. A larger boundary

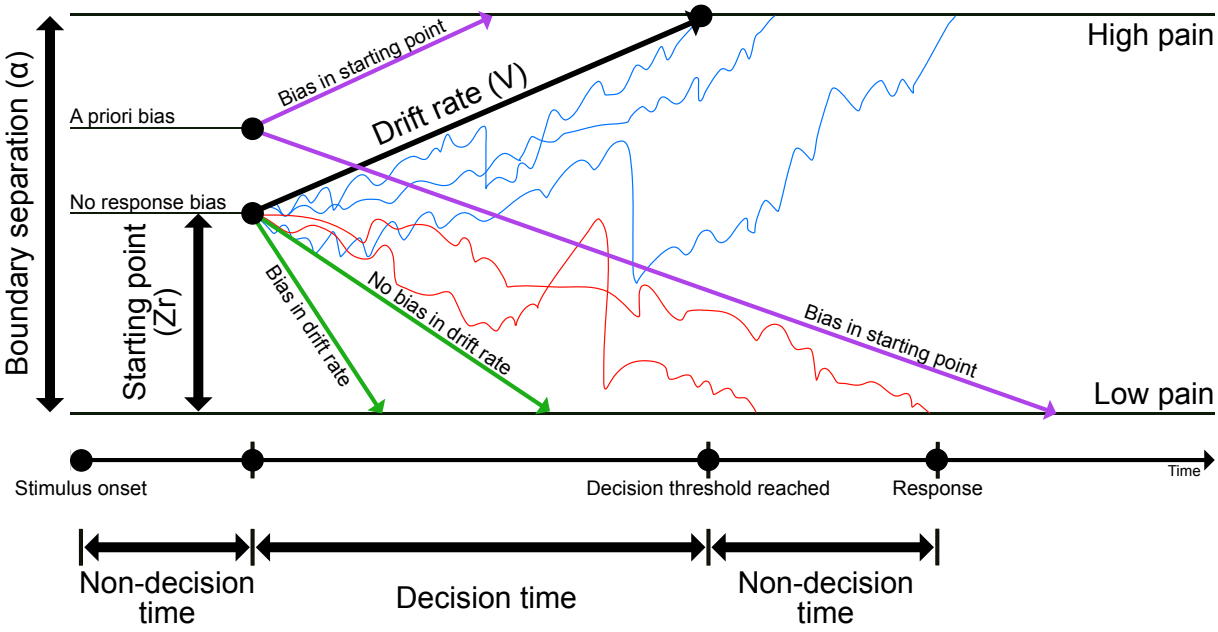


Figure 5.1: Schematic representation of DDM, modified from Becker et al. (2020) and Mulder et al. (2012). The DDM variables of interest of the present study with appropriate experimental paradigms are shown. Boundary separation (α) is the distance between lower (e.g., low pain) and upper (e.g., high pain) thresholds. Starting point (Z_r) is indicative of response bias. Drift rate (V) is a measure of sensory information processing. Blue lines represent trials where evidence accumulation led to high pain responses, and red lines represent trials where evidence accumulation led to low pain responses. These blue and red lines are also representing how noisy the information from the environment is. Green lines are theoretical examples of different bias in drift rate, and purple lines are theoretical examples of bias in starting point.

separation would result in a slower decision process, as more evidence is required to reach the decision threshold (Myers et al., 2022). However, accuracy is often higher as it is more difficult for random noise in the evidence accumulation process to reach the incorrect threshold (Lerche et al., 2020). A reduced boundary separation indicates faster response time but at a cost of a higher error rate. Boundary separation, therefore, implements a speed-accuracy trade-off (Forstmann et al., 2016).

Starting point (Z_r) is indicative of response bias, and ranges from 0 (position of lower decision threshold) to 1 (position of upper decision threshold; Forstmann et al., 2016; Myers et al., 2022). For example, if the starting point is 0.5, then it means there is no bias – a similar amount of evidence is required to reach either decision thresholds. However, if the starting point is 0.8, then less evidence is required to reach the upper decision threshold, and more evidence is required to reach the lower decision threshold. Two examples of starting points (neutral and

biased) are shown in Figure 5.1. Bias in the starting point results from expectation about the upcoming stimulus, and thus can result in biased perceptual decision-making (Wiech et al., 2014).

Drift rate (V) is a measure of information processing speed, or the rate at which evidence is accumulated in favour of one outcome or the other. It can be affected by task difficulty or participant ability (Forstmann et al., 2016; Myers et al., 2022). Thus, for "easy" tasks that have clear discriminable stimuli, the drift rate would be high (i.e., a steep slope), producing fast reaction times as the decision threshold is reached earlier in time. For "difficult" tasks that comprise of ambiguous stimuli, the drift rate would be low (i.e., more shallow slope), meaning reaction times would be slower (as it takes longer to reach decision thresholds) and more varied (due to a greater amount of noise and a longer period in which that noise may play a role in processing). Examples of different drift rates are shown in Figure 5.1.

Non-decision time (t_0) measures the processes necessary for encoding a stimulus and executing motor responses (Forstmann et al., 2016; Myers et al., 2022). Total response time is therefore the time from the starting point to reaching one of the boundary thresholds, plus the non-decision time.

In their study, Wiech et al. (2014) used DDM to examine the effect of two probabilistic cues (cue 1: 80% chance of receiving high pain, 20% chance of receiving low pain; cue 2: 50% chance of receiving either high or low pain) on pain perception and found that increased probabilities of outcomes (signalled by cues) resulted in biased starting points and faster drift rates for the expected outcome. More generally, DDMs have been used (primarily among neurotypical individuals) to study the effect of expectation (Wiech et al., 2014; Zaman et al., 2020; Zaman et al., 2022; Zhang et al., 2023), as well as the effect of reward (S. Becker et al., 2021) and emotion such as fear (Zaman et al., 2018) on pain perception. Studies have found a shift in starting point towards the expected response threshold (Wiech et al., 2014; Zaman et al., 2020), a faster drift rate for predictable outcomes (Wiech et al., 2014; Zaman et al., 2020), and a smaller decision threshold separation boundary when painful stimuli was applied compared to innocuous stimuli (Zaman et al., 2020).

Studies using DDM to investigate perceptual decision-making in the autistic population are

limited, provide mixed results, and none have used pain as stimulus (Manning et al., 2022; Pirrone et al., 2017; Powell et al., 2019). Studies have found wider boundary separation in both autistic children and adults compared to neurotypical counterparts (Iuculano et al., 2020; Karalunas et al., 2018; J. C. Kirchner et al., 2012; Manning et al., 2022; Pirrone et al., 2017; Pirrone et al., 2020), but also smaller boundary separation in autistic adolescents (Powell et al., 2019). While some studies document no difference in drift rate (Iuculano et al., 2020; Pirrone et al., 2017; Pirrone et al., 2020), other studies show slower drifts rate in autistic children (Karalunas et al., 2018) and adolescents (Powell et al., 2019) compared to neurotypical counterparts. The somewhat discordant results related to drift rate may be due to the co-occurring ADHD symptoms (Karalunas et al., 2018; Powell et al., 2019), stages of development (children vs. adolescents vs. adults), or the type of stimuli used (e.g., visual, motion, social, cognitive). No study has found group differences in non-decision time between autistic and non-autistic individuals.

Using DDM to study autistic perception is advantageous to investigate the Bayesian account of autism (Pellicano & Burr, 2012) because it separates the sensory processing (i.e., drift rate) and expectation effects (i.e., starting point) within a typical 2AFC task, where cues can be used to change expectations about upcoming stimuli. It is clear, however, that the evidence for the Bayesian account of autism is mixed (Goris et al., 2018; Karaminis et al., 2020; Lawson et al., 2017; Manning et al., 2017), with no clear insight as to which components (if any) of the Bayesian perceptual process are atypical. No study thus far has used DDM to investigate the effects of probabilistic cues on pain processing in autism, or to separate the effects of autism and alexithymia.

5.1.1 Goals and Hypotheses

The initial aim of this present study was to use pain stimuli and DDM to assess the influence of probabilistic expectations on pain perception in the autistic population. Additionally, the effect of probabilistic expectations on pain perception was contrasted with their effect on vision, an example of exteroceptive perception. Finally, the effect of probabilistic cues on pain and

visual perception was also investigated in alexithymia. These enable the Bayesian account of autism (Pellicano & Burr, 2012) to be tested in the interoceptive pain domain, the effect of autism on interoceptive and exteroceptive perception to be compared, and the effect of alexithymia to be determined. Under the alexithymia hypothesis (Brewer et al., 2015), the effects of alexithymia may be limited to the interoceptive domain.

In line with the findings from Wiech et al. (2014), it was hypothesised that there will be a bias in the drift rate and starting point for the cue with the unequal distribution of probabilistic outcomes (e.g., 80% chance of receiving high pain and 20% chance of receiving low pain) compared to the cue with an equal distribution of probabilistic outcomes (e.g., 50% chance of receiving high or low pain). It was also hypothesised that alexithymic traits, rather than autistic traits, would have an effect on variables computed by DDM, such as the starting point. This is based on the results from the previous chapters that suggest that alexithymic traits shape the mechanisms behind prediction formation and updating during pain perception.

5.2 Methods

5.2.1 Participants

Participants were recruited to take part in a study investigating the influence of autism and alexithymia on pain perception (Study 1) and visual perception (Study 2). The study was approved by the University of Oxford, Medical Sciences Interdivisional Research Ethics Committee, and all participants received an honorarium.

Common methodologies were used for participant recruitment and inclusion criteria as outlined in Section 3.2.1. For Study 2, participants were also recruited on Prolific (www.prolific.com; Prolific, 2020).

Study 1 (Pain)

87 adults (18 aut+alex, 15 aut-alex, 14 alex, 40 nt) participated in the study. Participants were removed from analyses if they met any of the following criteria: i) did not meet the inclusion

criteria, ii) had incomplete questionnaire data, iii) failed calibration, iv) failed cue check, or v) had more than 10% of the trials removed. Further details of the exclusion process can be found in Section A.4.1.

The final analysis sample, after applying the exclusion criteria, consisted of 76 adults (43 female, 7 other; age 23.8 ± 8.46). The number of participants per group can be found in Table 5.1.

Study 2 (vision)

Study 2 consisted of several online experiments to develop a visual version of the paradigm used in Study 1. Studies 2.1-2.4 were pilot experiments to develop the paradigm. Once the paradigm was finalised, Study 2.5 was conducted to test the main hypotheses. For the pilot experiments (Studies 2.1-2.4), only neurotypical participants were recruited. In addition to the exclusion criteria applied in Study 1 (pain), Study 2 (vision) participants were removed from analyses if they scored below 80% in i) practice trials, and ii) attention check trials within the main task, and iii) if they incorrectly responded to the question about the associations between cues at the end of the experiment (attention check questionnaire). Details of exclusion criteria application can be found in Section A.4.1. The number of participants for Studies 2.1-2.5 can be found in Table 5.1.

225 adults participated in Study 2.5. After applying the exclusion criteria, the final sample consisted of 148 adults (83 female, 2 other; age 27.5 ± 8.06).

Table 5.1: Summary of participants per group. Initial sample and final sample used for analyses after applying the exclusion criteria are listed. Participants were asked to identify their gender from three options: male, female, and other. There was no group structure for Studies 2.1-2.5.

Study	Stimulus	Group	Initial sample	Final sample			
				N	Mean ± SD age	Age range	Gender composition
1.0	Pain	aut+alex	18	15	31.5 ± 11.1	[18, 49]	8 male, 5 female, 2 other
		aut-alex	15	11	27.9± 11.20	[18, 48]	7 male, 2 female, 3 other
		alex	14	13	21.2 ± 5.13	[18, 34]	12 female, 1 other
		nt	40	36	20.2 ± 2.83	[18, 28]	11 male, 24 female, 1 other
2.1	Vision		60	38	24.9 ± 9.15	[18, 50]	17 male 21 female
2.2			47	38	32.1 ± 10.2	[19, 50]	12 male, 26 female
2.3			7	4	33.0 ± 10.7	[26, 49]	1 male, 3 female
2.4			8	3	28.3 ± 9.29	[22, 39]	1 male, 2 female
2.5			225	148	27.5 ± 8.06	[18, 49]	63 male, 83 female, 2 other

5.2.2 Measures and Procedure

Questionnaire measures

The following self-report questionnaires were used to assess how various traits affect the magnitude of the cue effect: AQ-50 (autistic traits; Baron-Cohen et al., 2001), TAS-20 (alexithymic traits; Bagby et al., 1994), STAI-1, and STAI-2 (state and trait anxiety; Spielberger et al., 1983), BDI-II (depressive traits; Beck et al., 1996), PCS (pain catastrophising; Sullivan et al., 1995), IAS (interoceptive accuracy; Murphy et al., 2019), and IATS (interoceptive attention; Gabriele et al., 2022).

For Study 1 (pain), BPQs-A (bodily awareness; Porges, 1993), IUS-12 (intolerance of uncertainty; Wilson et al., 2020), and FSIQ (cognitive abilities; Wechsler, 2011) were also quantified. For Study 2, participants had the option to complete IUS-12 and the MR sub-test of WASI-II (Wechsler, 2011). For an overview of these questionnaires, see Section 3.2.1.

Stimuli and calibration

Pain stimuli (Study 1) The calibration procedure was completed as outlined in Section 3.2.1. Target stimulations were set as 2 ("perceptible") and 8 out of 10 ("definitely uncomfortable, but tolerable") on a verbally reported pain scale. These pain levels were chosen based on Wiech et al. (2014)'s study. The chosen levels were then delivered in a pseudo-randomised order and participants were instructed to identify the intensity of each stimulation. The process continued until the participants were consistent in their ratings at least twice in a row. Level 2 pain is hereafter referred to as low pain, and level 8 as high pain.

Visual stimuli (Study 2) Square greyscale images of varying intensities (Figure 5.2) were used as visual stimuli, created using MATLAB (The MathWorks Inc., 2022). A total of 256 images of uniform intensity were created, ranging from white (intensity 256) to black (intensity 0). For Studies 2.1 and 2.2 (stimuli range: 190 to 60), task performance (accuracy) was very high, so the range was made smaller for Study 2.3 (stimuli range: 165 to 95). The stimuli range was finalised between 155 and 105 for Studies 2.4 and 2.5. Examples of the stimuli can be found

in Figure 5.2.



Figure 5.2: Examples of visual stimuli (from left to right): intensity 190, 165, 155, 105, 95, and 60. Studies 2.1 and 2.2 used intensity 190 (far left) through 60 (far right), Study 3 used intensity 165 (second from left) through 95 (second from left), and Studies 2.4 and 2.5 used intensity 155 (centre left) through 105 (centre right).

During the calibration, participants were shown a series of grey images of varying intensity levels, and were asked to rate each image on a scale from 0 (light) to 10 (dark). They were first shown what images that correspond to 0 and 10 looked like. Images were presented in a random order (i.e., the images did not progressively increase or decrease in darkness), and participants were made aware of this fact. Participants were told that images that they rate as 2 and 8 will be used later in the task, and were therefore encouraged to ensure that they rate at least one image as 2 or 8. Level 2 image is hereafter referred to as light (low) image, and level 8 as dark (high) image.

The number of images participants had to rate differed depending on the study, due to the difference in the range of grey images used. Participants rated 27 images for Studies 2.1 and 2.2, 15 images for Study 2.3, and 11 images for Studies 2.4 and 2.5.

Discrimination task

In Study 2 (vision), to ensure that levels 2 and 8 could be discriminated, participants underwent a discrimination task following calibration. 10 images of levels 2 and 8 stimuli (20 trials in total) were presented in a random order, and participants were asked to indicate whether the stimulus presented was level 2 or 8. If participants rated multiple images as 2 or 8 in the calibration, then the average of those images were presented. If participants failed to rate any of the images as either 2 or 8, then no picture was presented, and there was a response option of "No picture." Failure to meet the passing threshold of 80% led participants to repeat calibration, up to a total of three attempts.

Participants did not complete this task in Study 1 (pain), as this was performed during the

calibration process.

Cue check task

The cue check task was conducted to ensure that participants had the correct understanding of the associations between the cue (circle or triangle) and their corresponding probabilistic outcomes. Participants were told that when they see a circle, there is a 80% chance that the upcoming stimulus level is high intensity and a 20% chance that it is low intensity (80/20 condition). If they saw a triangle, then the probabilities of receiving high or low intensity are 50% (50/50 condition). Each cue was presented ten times in a randomised order (20 trials total), and participants were required to indicate the probability of receiving high intensity stimulus after seeing the shape that was presented. Participants were required to achieve over 80% accuracy before moving on to practice trials, with up to three attempts.

Probabilistic cueing Task

The probabilistic cueing task (Wiech et al., 2014) was explained to participants as a task where cues presented had probabilistic outcomes regarding the upcoming stimuli. It was a 2AFC task, in which two cues (circle and triangle) with two possible outcomes each, were presented. One cue represented an 80% chance of the high stimulus (pain or visual stimulus) and 20% chance of the low stimulus, while the other cue indicated an equal chance of receiving the high or low stimulus. Decision accuracy and reaction time were recorded as variables of interest.

Study 1 (pain) As shown in Figure 5.3, each trial began with the presentation of fixation cross for a second, cue presentation (circle or triangle, 0.5 seconds), anticipation period (4-6 seconds), stimulation delivery (0.2 seconds), and a cool-down period (4-6 seconds). Immediately after the stimulation delivery and during the cool-down period, participants were instructed to respond as accurately and as quickly as possible in deciding whether the pain stimulus was high or low intensity, by pressing one of two keys (j or f) with their right hand. No feedback was given regarding their decision accuracy. If participants did not make a response before the next fixation cross presentation (within 4-6 seconds), that trial was marked as "No response." The experiment

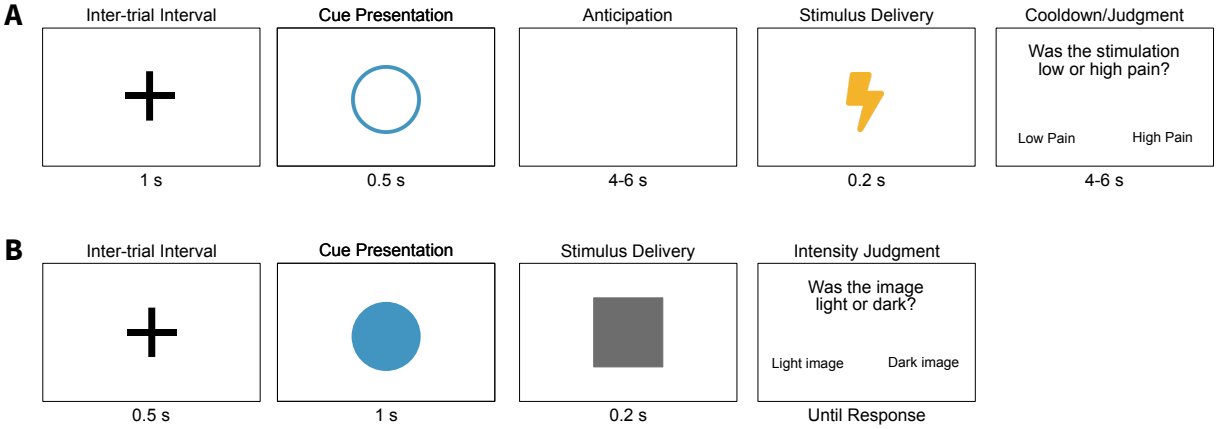


Figure 5.3: Probabilistic cueing task trial structure for (A) Study 1 using pain stimuli, and (B) Study 2 using visual stimuli. (A) For Study 1 (pain), after an inter-trial interval (1 s), a cue indicating probabilistic outcomes (circle: 80/20 condition, triangle: 50/50 condition) was presented (0.5 s). This was followed by an anticipation period (4-6 s), stimulation delivery (0.2 s), and a cool-down period (4-6 s). Immediately after the stimulation delivery, participants were instructed to respond as accurately and as quickly as possible by using one of two keys to indicate whether the stimulation they received was high or low pain. Study 1 (pain) consisted of 4 blocks of 40 trials, with self-timed breaks between blocks. (B) For Study 2 (vision), the same paradigm without anticipation and cool-down periods were used. Study 2 (vision) also included attention checks, where the cues were filled (as shown in B), rather than unfilled (as shown in A). When cues were filled, participants were instructed to indicate whether the shape they saw was circle or triangle. In the final version, Study 2.5 (vision) consisted of 5 blocks of 60 trials and 4 attention check trials.

consisted of 4 blocks of 40 trials, with a self-timed break in-between blocks. The order of conditions was pseudo-randomised in each block, with up to two consecutive repetitions of the same condition. Prior to starting the main task, participants underwent 16 practice trials (eight 80/20 and eight 50/50 trials) before the main task. Participants had the opportunity to ask any questions before starting the main experiment. The trial composition is shown in Table 5.2.

Study 2 (vision) A similar paradigm to Study 1 (pain) was used, with a few modifications. As shown in Figure 5.3, each trial began with a presentation cross (0.5 seconds), cue presentation (circle or triangle, 1 second), and stimulation delivery (0.2 seconds). Trials moved on as soon as participants made a response after stimulus presentation. As in Study 1 (pain), participants were instructed to respond as accurately and quickly as possible whether the image was dark or light, by pressing one of the two keys (p or q). No feedback was given regarding their decision accuracy. In addition, attention checks were interspersed within the main task. In attention check trials, cue shapes were filled, and no stimulus was presented. Participants were asked if the image they saw was a circle or a triangle, by pressing one of the two keys (f or j). As in Study 1 (pain), the order of conditions was pseudo-randomised in each block, with up to two

consecutive repetitions of the same condition. Participants also underwent practice trials prior to starting the main task. The final version, Study 2.5 (vision), consisted of 5 blocks of 60 trials and 6 attention checks with self-timed breaks between blocks.

Paradigm development (vision) The vision paradigm started by using the same number of trials as Study 1 (pain), which consisted of 16 practice trials (8 trials per trial types) and 40 main trials (20 trials per trial type). 4 attention check trials (2 trials per trial type) were also added as this was an online experiment. In subsequent studies, the number of blocks and trials were increased, in addition to adjusting the range of stimuli (as described in Section 5.2.2). The justification was that visual stimuli are less salient signals than pain, and therefore may require more trials due to decreased power. Table 5.2 shows the trial breakdown for Studies 2.1 through 2.5.

Table 5.2: Trial composition for the probabilistic cueing task. For Study 1 (pain), trial composition was based on Wiech et al. (2014)'s paradigm, and consisted of 4 blocks of 40 trials. Study 2 (vision) trial composition was modified from Study 1 (pain), and included attention check trials. The final version (Study 2.5) consisted of 5 blocks of 60 trials and 6 attention checks trials.

Study	Stimulus	Practice trials		Number of blocks	Main task Number of trials		Attention check trials	
		80/20	50/50		80/20	50/50	Circle	Triangle
1	Pain	8	8	4	20	20	-	-
2.1	Vision	8	8	5	20	20	2	2
2.2		8	8	5	30	30	3	3
2.3		40	40	5	30	30	3	3
2.4		40	40	5	30	30	3	3
2.5		40	40	5	30	30	3	3

Procedure

Study 1 (pain) Prior to the experimental session, participants were asked to read the participant information sheet and complete demographic information, AQ-50, TAS-20, BPQs-A, IAS, and IUS-12. At the experimental session, after giving informed consent and confirming demographic information, participants were seated in a quiet room. The pain stimulation delivery device was placed on the participant's right forearm. Pain calibration started immediately after to determine the necessary pain stimulation levels. Participants then completed the STAI-1 questionnaire,

then took part in the cue check task and the probabilistic cueing task. Upon completion of the probabilistic cueing task, electrodes were removed, and participants completed the WASI-II, STAI-2, BDI-II, PCS, and IATS. The probabilistic cueing task took approximately 30 minutes to complete, and the study session lasted approximately an hour and a half. Questionnaires were presented on Gorilla (www.gorilla.sc; Anwyl-Irvine et al., 2020), and the order of questionnaires was randomised. Experimental tasks (calibration, cue check, practice and main trials of the probabilistic cueing task) were presented using PsychoPy (v2022.2.5; Peirce et al., 2019).

Study 2 (vision) After giving informed consent, participants completed demographic information, AQ-50, TAS-20, IAS, and IATS. They then completed a calibration, followed by the discrimination task. This was followed by the cue check task, STAI-1, practice trials, and then the main probabilistic cueing task. Upon completion of the probabilistic cueing task, participants completed the STAI-2, BDI-II, PCS, and the attention check questionnaire. Participants were given the opportunity to also complete the IUS-12 and the MR sub-test of the WASI-II for extra payment, but these were optional due to financial and time constraints. Participants were required to score above 80% in all tasks (discrimination task, cue check task, and practice trials) before continuing to the next steps. If they failed to meet the required threshold after three attempts, participants were partially compensated and rejected from the study. Questionnaire order was randomised. A time limit of 24 hours was imposed, to ensure that participants completed it in one sitting. Device type was restricted to computers and browser was limited to Chrome, to ensure stimuli would be presented without delays. The study session took approximately 50 minutes. Study was hosted and presented online on Gorilla (www.gorilla.sc; Anwyl-Irvine et al., 2020).

5.2.3 Statistical Analyses

All statistical analyses were performed using R (R Core Team, 2022) and RStudio (version 2023.06.0+421; RStudio Team, 2022), with a statistical threshold of $p < .05$. The same statistical analyses were applied to Studies 1 and 2.5. The definitions of stimulus type and corresponding condition types used per study are summarised in Table 5.3. Prior to analyses, any trials where i)

the experimenter failed to change the stimulation level to the appropriate one, ii) the participant did not make a response, or iii) the absolute z-score transformed reaction time (per group, per condition) was greater than 3 were removed. If participants had more than 10% of the trials removed, then they were removed completely from all analyses (Study 1 (pain): 5 participants, Study 2.5 (vision): 11 participants). Further details about trial-related exclusion can be found in Section A.4.1. Autistic and alexithymic participants were invited to take part in Study 2.5, but as the majority of these participants failed to complete the study, no group comparisons (aut+alex, aut-alex, alex, and nt groups) were performed.

Four trial types (or conditions) were present in the experimental paradigm: i) 80/20 cue, high stimulus (80/20 high), ii) 80/20 cue, low stimulus (80/20 low), iii) 50/50 cue, high stimulus (50/50 high), iv) 50/50 cue, low stimulus (50/50 low). Comparisons were conducted on variables between i) the 80/20 and 50/50 high conditions to assess the cue effect, and ii) 50/50 high and low conditions to assess the effect of stimulus intensity. While data for the 80/20 low condition was processed (and therefore shown in some figures for illustrative purposes), it was not used in any of the data analysis due to the small number of trials (Study 1 (pain): 16 trials, Study 2.5 (vision): 30 trials).

Table 5.3: Description of stimuli used in Study 1 (pain) and Studies 2.1-2.5 (vision). High stimulation level means 8/10 on either pain (Study 1) or vision (Study 2) scale, and low stimulation level means 2/10 on either pain (Study 1) or vision (Study 2) scale. The probabilistic outcomes associated with cues were the same for all studies.

	Stimulation level		80/20		50/50	
	High (8/10)	Low (2/10)	P(High)	P(Low)	P(High)	P(Low)
Study 1 Studies 2.1-2.5	High pain Dark image	Low pain Light image	80%	20%	50%	

Accuracy and reaction time

To investigate the effect of cue and outcome, paired samples Wilcoxon tests (as the difference between conditions were not normally distributed) were performed to assess whether there were differences in accuracy, mean reaction time, and reaction time variability between conditions. The following comparisons were assessed: i) for high stimuli between the 80/20 and 50/50 conditions, and ii) between high and low stimuli in the 50/50 condition.

Difference scores Difference scores (accuracy, mean reaction time, reaction time variability) between the 80/20 and 50/50 high conditions were calculated as a measure of the cue effect. These three variables will now be referred to as cue effect variables. To assess if there were group or individual differences in the cue effect variables, Kruskal-Wallis test and non-linear mixed effects (NLME) model were used. Kruskal-Wallis test was performed to explore any group effects in Study 1 (pain; aut+alex, aut-alex, alex, and nt groups), and NLME was used to see if autistic (AQ-50) or alexithymic traits (TAS-20) modulated the cue effect variables. AQ-50, TAS-20, and their interaction term were added as predictors, with participants as random intercept.

Drift diffusion model

DDM was performed to assess the differences between conditions (80/20 high, 50/50 high, 50/50 low) in i) the boundary separation (α), ii) the starting point (Z_r), and iii) the drift rate (V). These three variables will now be referred to as DDM variables. DDM was performed using fast-dm software (Voss et al., 2015), and was fitted per individual. This therefore resulted in 9 variables (three variables per three conditions) per participant. Reaction times were log-transformed and centred to check for outliers within participants. Analysed responses indicated whether participants identified the delivered stimuli as high (1) or low (0), and the corresponding reaction time. Overall, 1.37% ± 1.82% of trials were removed for Study 1 (pain) participants, and 2.32% ± 2.17% for Study 2.5 (vision) participants. Further details about trial removal can be found in Section A.4.1.

The following parameters were set as the current studies (Studies 1 and 2.5) would constitute as having small to medium trial numbers (< 500). First, the Kolmogorov-Smirnov approach was chosen as the optimisation criterion as i) a more robust procedure was required, and ii) it was not known whether the data were contaminated. Its characteristics can be seen as a compromise between maximum likelihood and chi-square based methods (Voss et al., 2015). Second, precision was set to 3.0 and non-decisional constant (t_0) was set to 0.3, which were default settings. Third, inter-trial variability of starting point (S_{zr}), drift (S_v), and non-decisional constant (S_{t0}), as well as the difference in non-decisional constant (d) were set to 0, to make

the estimation of the other parameters more robust (Voss et al., 2015). Additionally, previous literature found no differences in non-decision time between autistic and non-autistic groups (Pirrone et al., 2020; Powell et al., 2019), and the study that is being replicated for this present study found no effect of condition on non-decision time (Wiech et al., 2014).

After obtaining DDM variables, and prior to any further analysis involving DDM variables, any statistical outliers per condition were removed (third quartile ± 1.5 × inter-quartile range). Kruskal-Wallis test, and where appropriate, Dunn's test, were performed using Bonferroni correction to test the significance of the effect of condition on the three DDM variables. For Study 1 (pain), the effect of group was also explored.

Elastic net

To assess the effect of individual differences on the variables of interest, elastic net regressions were performed. The aims were two-fold: to test whether i) cue effect variables (accuracy, mean reaction time, and reaction time variability), and ii) DDM variables (α, Z_r, V) were modulated by autistic and alexithymic traits, and other nuisance covariates. An elastic net approach was chosen due to the small sample size relative to the number of predictors and the high correlation among the self-report questionnaire measures. Elastic net analysis was conducted using glmnet (Friedman et al., 2010) and caret (Kuhn, 2008) packages, using the cross-validation method. All variables were centred prior to analysis. If the variables were not normally distributed, they were transformed according to the λ of the Box-Cox transformation function (Box & Cox, 1964; log transformation was deemed appropriate for all since $-0.5 < \lambda < 0.5$), then centred. A constant of 10 was added to all variables prior to log transformation to avoid getting negative infinity values.

Independent variables were all self-report questionnaire measures. As IUS-12 and MR were optional for Study 2.5 (vision), those with missing IUS-12 or MR data were excluded from this analysis. λ value was selected as the largest λ that gives the most regularised model, at which the mean of squared errors (MSE) is within 1 standard error of the smallest MSE.

Cue effect variables Elastic net was performed on the cue effect variables (the difference between the 80/20 and 50/50 high conditions in accuracy, mean reaction time, and reaction time variability), resulting in three models per study (six models total).

DDM variables Elastic net was performed on i) the boundary separation (α), ii) the starting point (Z_r), and iii) the drift rate (V) per condition (80/20 high, 50/50 high, 50/50 low), and iv) the difference in DDM variables (α, Z_r, V) between the 80/20 and 50/50 high conditions, resulting in 12 models per study (24 total).

5.3 Results

5.3.1 Descriptive Statistics

Table 5.4 summarises the demographic information for participants that were analysed in Studies 1 and 2.5.

Group comparisons of self-report measures for Study 1 (pain)

Group comparisons found that the aut+alex group was significantly older, had higher autistic, alexithymic, anxious (state and trait), depressive, pain catastrophising, and intolerance of uncertainty traits, and had less interoceptive accuracy than the nt group. The aut+alex group was older, and had higher autistic traits than the alex group. The aut-alex had higher autistic traits than the nt group. The alex group had higher autistic, anxious (trait), depressive, and intolerance of uncertainty traits than the nt group. Further details of group comparisons can be found in Section A.4.2.

Table 5.4: Descriptive statistics for self-report measures for Studies 1 (pain) and 2.5 (vision). IUS-12 and MR were optional for Study 2.5 (vision) participants, so the proportions of the missing data are shown as result. The full FSIQ was not obtained for Study 2.5 (vision), only the MR sub-scale T-score (MR T-score). BPQs-A was not collected for Study 2.5. * $p < .05$, ** $p < .01$, *** $p < .001$.

	Study 1 (pain)					**Study 2 (vision)**
	aut+alex (n = 15)	aut-alex (n = 12)	alex (n = 13)	nt (n = 36)	Overall (N = 76)	(N = 148)
Age						
Mean (SD)	31.5 (11.1)	27.9 (11.2)	21.2 (5.13)	20.2 (2.83)	23.8 (8.46)	27.5 (8.06)
Median [Min, Max]	26.0 [18.0, 49.0]	21.5 [18.0, 48.0]	19.0 [18.0, 34.0]	19.0 [18.0, 28.0]	20.0 [18.0, 49.0]	25.0 [18.0, 49.0]
	Comparisons: * alex < aut+alex, *** nt < aut+alex					
Gender						
Male, female, other (N)	8, 5, 2	7, 2, 3	0, 12, 1	11, 24, 1	26, 43, 7	63, 83, 2
Male, female, other (%)	53.3, 33.3, 13,3	58.3, 16.7, 25.0	0, 92.3, 7.7	30.6, 66.7, 2.8	34.2, 56.6, 9.2	42.6, 56.1, 1.4
Other						
AQ-50						
Mean (SD)	38.4 (6.10)	29.4 (8.16)	26.0 (9.50)	20.0 (8.26)	26.1 (10.6)	31.1 (10.1)
Median [Min, Max]	37.0 [31.0, 49.0]	32.0 [18.0, 40.0]	26.0 [12.0, 47.0]	19.0 [8.00, 40.0]	25.5 [8.00, 49.0]	33.5 [2.00, 49.0]
	Comparisons: * alex < aut+alex, *** nt < aut+alex, * nt < aut-alex					
TAS-20						
Mean (SD)	67.4 (7.81)	47.4 (10.7)	68.8 (6.53)	42.1 (7.83)	52.5 (14.5)	47.9 (12.4)
Median [Min, Max]	64.0 [61.0, 91.0]	49.5 [24.0, 60.0]	67.0 [61.0, 82.0]	43.0 [24.0, 60.0]	51.5 [24.0, 91.0]	47.0 [20.0, 91.0]
	Comparisons: ** aut-alex < aut+alex, ** aut-alex < alex, *** nt < aut+alex, *** nt < alex					
STAI-1						
Mean (SD)	43.4 (11.6)	33.4 (9.14)	37.8 (7.24)	31.5 (11.2)	35.2 (11.2)	37.8 (12.7)
Median [Min, Max]	41.0 [30.0, 74.0]	34.5 [21.0, 49.0]	37.0 [28.0, 53.0]	32.5 [0, 50.0]	36.0 [0, 74.0]	35.0 [20.0, 76.0]
	Comparisons: *** nt < aut+alex					
STAI-2						
Mean (SD)	58.7 (6.64)	50.9 (11.3)	58.2 (9.62)	43.7 (9.44)	50.3 (11.4)	46.8 (11.6)
Median [Min, Max]	58.0 [44.0, 70.0]	54.5 [35.0, 67.0]	61.0 [31.0, 69.0]	45.0 [29.0, 64.0]	51.0 [29.0, 70.0]	47.0 [23.0, 75.0]
	Comparisons: *** nt < aut+alex, *** nt < alex					
BDI-II						
Mean (SD)	16.5 (9.16)	13.3 (9.55)	16.4 (6.78)	9.69 (5.92)	12.8 (7.90)	12.1 (8.83)
Median [Min, Max]	17.0 [4.00, 38.0]	13.5 [0, 28.0]	15.0 [6.00, 32.0]	8.00 [0, 27.0]	12.0 [0, 38.0]	11.0 [0, 40.0]
	Comparisons: * nt < aut+alex, * nt < alex					
PCS						
Mean (SD)	29.8 (9.25)	24.5 (10.5)	25.4 (13.3)	19.4 (9.99)	23.3 (11.1)	23.6 (11.9)
Median [Min, Max]	29.0 [16.0, 50.0]	24.5 [11.0, 41.0]	23.0 [5.00, 51.0]	20.0 [3.00, 43.0]	23.0 [3.00, 51.0]	24.0 [0, 51.0]
	Comparisons: * nt < aut+alex					
BPQs-A						
Mean (SD)	53.2 (7.39)	55.1 (9.97)	56.6 (6.30)	52.9 (9.35)	53.9 (8.60)	
Median [Min, Max]	54.2 [39.3, 66.1]	55.9 [40.1, 69.1]	55.1 [49.6, 68.3]	56.0 [34.2, 71.3]	55.5 [34.2, 71.3]	
IAS						
Mean (SD)	55.3 (12.8)	65.3 (14.1)	65.5 (11.3)	71.4 (11.3)	66.3 (13.3)	81.2 (12.8)
Median [Min, Max]	54.0 [37.0, 82.0]	73.0 [39.0, 85.0]	67.0 [44.0, 86.0]	70.5 [49.0, 100]	67.0 [37.0, 100]	80.0 [38.0, 104]
	Comparisons: *** aut+alex < nt					
IATS						
Mean (SD)	46.1 (12.0)	42.6 (15.0)	45.8 (10.7)	45.3 (11.9)	45.1 (12.1)	47.6 (16.2)
Median [Min, Max]	46.0 [22.0, 63.0]	39.0 [28.0, 80.0]	49.0 [30.0, 62.0]	44.5 [24.0, 72.0]	45.0 [22.0, 80.0]	47.0 [21.0, 95.0]
IUS-12						
Mean (SD)	42.9 (7.93)	38.3 (9.26)	41.6 (8.00)	32.3 (7.14)	36.9 (8.95)	37.7 (8.82)
Median [Min, Max]	45.0 [28.0, 54.0]	38.0 [18.0, 54.0]	43.0 [23.0, 52.0]	31.5 [20.0, 47.0]	37.5 [18.0, 54.0]	38.0 [14.0, 59.0]
Missing (%)						25 (16.9%)
	Comparisons: *** nt < aut+alex, ** nt < alex					
FSIQ (MR T-score for Study 2.5)						
Mean (SD)	123 (13.9)	125 (11.8)	124 (12.8)	118 (9.23)	121 (11.5)	54.3 (8.44)
Median [Min, Max]	121 [99.0, 152]	122 [109, 148]	121 [106, 150]	117 [106, 150]	120 [99.0, 152]	54.0 [32.0, 75.0]
Missing (%)						25 (16.9%)

5.3.2 Condition and Group Differences in Task Performance

Task performance (accuracy and reaction time) is shown in Figure 5.4. Paired Wilcoxon tests were performed to assess the differences in accuracy and reaction time (mean reaction time and reaction time variability) as a way to confirm the presence of a cue effect. Mean values for task performance can be found in Table 5.5.

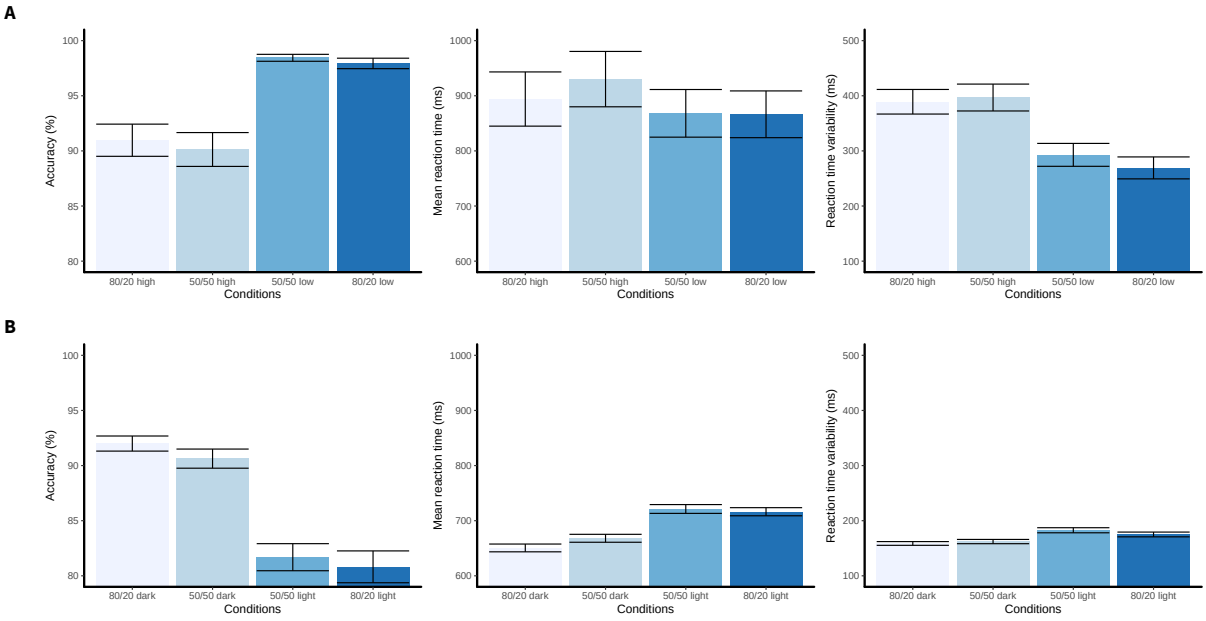


Figure 5.4: Task performance per condition for (A) Study 1 using pain stimuli, and (B) Study 2.5 using visual stimuli. Bar plots show (left) accuracy, (middle) mean reaction time, and (right) reaction time variability. 80/20 indicates participants saw a cue with a probabilistic value of 80% chance of receiving high pain/seeing a dark image and 20% chance of receiving low pain/seeing a light image after cue presentation. 50/50 indicates participants saw a cue with a probabilistic value of 50% chance of receiving high or low pain/seeing dark or light image after cue presentation. High or low indicates the intensity of the pain stimuli participants received, and dark or light indicates the intensity of the image the participant saw.

Study 1 (pain)

Of the 76 participants that were analysed, 27 people (35.53%) scored above 95% in all four conditions. A minority of participants (n = 8, 10.53%) scored above 95% in one condition or less. Accuracy rates were higher for low pain than high pain in the 50/50 condition [V = 154.5, $p < .001$]. There was no significant difference in accuracy for high pain between the 80/20 and 50/50 conditions [V = 830.5, p = .114], providing no evidence for an effect of the cue on perception of high pain.

Table 5.5: Means of task performance variables for Studies 1 (pain) and 2.5 (vision). Sample size per group is shown for Study 1 (pain). Study 2.5 (vision) did not have a group structure. Cue effect variables have different sample numbers as outliers specific to this analysis were removed prior to analyses.

			Accuracy (%)			Reaction time (ms)					
						Mean			Variability		
	Study	Group	*N*	Mean (SD)	Median [Min, Max]	*N*	Mean (SD)	Median [Min, Max]	*N*	Mean (SD)	Median [Min, Max]
80/20 high	Study 1 (pain)	aut+alex	15	95.5 (7.99)	98.4 [75.0, 100]	15	739 (385)	589 [285, 1520]	15	374 (241)	305 [68.9, 842]
		aut-alex	12	95.1 (7.98)	100 [73.4, 100]	12	782 (318)	769 [320, 1420]	12	344 (169)	354 [72.0, 679]
		alex	13	87.3 (16.1)	95.3 [45.3, 100]	13	778 (365)	736 [379, 1530]	13	368 (179)	326 [136, 736]
		nt	36	89.0 (13.7)	95.3 [50.8, 100]	36	1040 (465)	969 [264, 2100]	36	419 (190)	420 [68.1, 785]
		Overall	76	91.0 (12.7)	96.9 [45.3, 100]	76	894 (429)	811 [264, 2100]	76	389 (195)	366 [68.1, 842]
	Study 2.5 (vision)		148	92.0 (8.33)	95.0 [55.3, 100]	148	651 (85.8)	643 [442, 1000]	148	159 (41.1)	158 [66.7, 332]
50/50 high	Study 1 (pain)	aut+alex	15	94.1 (7.85)	97.5 [75.0, 100]	15	764 (388)	625 [309, 1680]	15	372 (234)	337 [71.0, 954]
		aut-alex	12	90.6 (12.1)	96.2 [62.5, 100]	12	848 (348)	757 [397, 1550]	12	399 (257)	373 [87.8, 1060]
		alex	13	88.8 (17.5)	95.0 [40.0, 100]	13	782 (364)	713 [412, 1560]	13	310 (132)	294 [107, 530]
		nt	36	88.8 (14.1)	93.8 [38.5, 100]	36	1080 (471)	968 [278, 2240]	36	438 (208)	404 [65.6, 853]
		Overall	76	90.1 (13.4)	97.4 [38.5, 100]	76	930 (438)	865 [278, 2240]	76	397 (213)	351 [65.6, 1060]
	Study 2.5 (vision)		148	90.6 (10.6)	94.0 [38.3, 100]	148	668 (87.6)	664 [465, 1010]	148	162 (47.0)	158 [54.9, 296]
50/50 low	Study 1 (pain)	aut+alex	15	98.5 (1.61)	97.5 [94.9, 100]	15	854 (457)	760 [370, 1990]	15	337 (250)	294 [121, 1010]
		aut-alex	12	95.8 (5.15)	97.5 [85.7, 100]	12	760 (238)	775 [446, 1330]	12	210 (117)	216 [74.0, 387]
		alex	13	98.8 (2.20)	100 [92.5, 100]	13	709 (256)	655 [408, 1280]	13	233 (121)	206 [111, 479]
		nt	36	99.2 (1.48)	100 [94.9, 100]	36	968 (396)	956 [344, 1990]	36	324 (174)	274 [75.4, 705]
		Overall	76	98.4 (2.74)	100 [85.7, 100]	76	868 (377)	794 [344, 1990]	76	293 (181)	242 [74.0, 1010]
	Study 2.5 (vision)		148	81.7 (14.9)	85.7 [25.0, 100]	148	721 (97.1)	715 [494, 1040]	148	183 (55.9)	188 [59.7, 337]
Difference (80/20 - 50/50 high)	Study 1 (pain)	aut+alex	15	1.37 (3.47)	1.00 [-3.23, 11.3]	15	-24.7 (66.4)	-23.9 [-159, 92.4]	15	1.54 (110)	11.6 [-178, 176]
		aut-alex	11	3.53 (4.88)	2.56 [-4.69, 11.2]	12	-66.3 (79.8)	-39.1 [-191, 50.2]	11	-26.2 (151)	-20.4 [-229, 194]
		alex	12	-0.525 (4.69)	-0.938 [-7.50, 9.06]	12	-24.5 (75.9)	-25.7 [-201, 56.2]	12	25.6 (101)	33.3 [-210, 201]
		nt	33	0.782 (3.94)	0 [-7.02, 8.75]	36	-42.5 (89.5)	-30.9 [-220, 118]	35	-6.70 (119)	1.57 [-218, 226]
		Overall	71	1.11 (4.22)	0 [-7.50, 11.3]	75	-39.9 (81.4)	-32.5 [-220, 118]	73	-2.64 (118)	2.57 [-229, 226]
	Study 2.5 (vision)		136	0.731 (3.83)	0.465 [-8.38, 10.9]	140	-16.3 (31.3)	-14.5 [-91.9, 59.4]	146	-3.48 (32.7)	-3.59 [-91.8, 69.5]

Mean reaction time was faster in the 80/20 than 50/50 condition for high pain [V = 2086, p = .001], providing an evidence of a cue effect for high pain, but no difference in reaction time variability was found [V = 1516, p = .786]. Mean reaction time was faster in low pain than high pain in the 50/50 condition [V = 1936, p = .014], and reaction time variability was also smaller in low pain than high pain in the 50/50 condition [V = 2248, $p < .001$], indicating an effect of stimulus intensity.

Study 2.5 (vision)

Of the 148 participants that were analysed, 7 people (4.73%) scored above 95% in all four conditions. The majority of participants (n = 88, 59.46%) only scored above 95% in one condition or less.

Accuracy rates were higher for dark images i) in the 80/20 than 50/50 condition [V = 3982, p = .019], and ii) than light images in the 50/50 condition [V = 7697.5, $p < .001$], with the difference between dark images indicating an effect of the probabilistic cue.

Mean reaction time was faster in the 80/20 than 50/50 condition for dark images [V = 8390, p

$< .001$], providing evidence of a cue effect for the dark image, but no difference in reaction time variability was found [$V = 6060$, $p = .296$]. Mean reaction time was faster for dark than light images in the 50/50 condition [$V = 1298$, $p < .001$], and reaction time variability was smaller for dark than light images in the 50/50 condition [$V = 3232$, $p < .001$], indicating an effect of stimulus intensity.

Group differences

No significant effect of group was found on accuracy in any of the conditions: i) the 80/20 high condition [$\chi^2(3) = 6.77$, $p = .080$], ii) the 50/50 high condition [$\chi^2(3) = 0.951$, $p = .813$], and iii) the 50/50 low condition [$\chi^2(3) = 6.35$, $p = .096$].

Significant effect of group on mean reaction time was found in the 50/50 high condition [$\chi^2(3) = 9.63$, $p = .022$], but there were no significant pair-wise comparisons. No significant effect of group on mean reaction time was observed in the 80/20 high condition [$\chi^2(3) = 7.52$, $p = .057$], nor in the 50/50 low condition [$\chi^2(3) = 6.08$, $p = .108$].

No significant effect of group on reaction time variability was found in the 80/20 high condition [$\chi^2(3) = 2.12$, $p = .548$], in the 50/50 high condition [$\chi^2(3) = 4.44$, $p = .218$], or in the 50/50 low condition [$\chi^2(3) = 5.69$, $p = .128$].

5.3.3 Group and Individual Differences in Cue Effect Variables

Difference scores between the 80/20 and 50/50 high conditions were computed for task performance variables (accuracy, mean reaction time, reaction time variability) as a measure of the cue effect to assess group (Study 1 (pain): aut+alex, aut-alex, alex, and nt groups) and individual differences (Studies 1 and 2.5).

Group differences in cue effect variables

Group comparisons were only performed for Study 1 (pain), as Study 2.5 (vision) did not have a group structure. Kruskal-Wallis test found no significant effect of group on accuracy difference [$\chi^2(3) = 4.95$, $p = .175$], mean reaction time difference [$\chi^2(3) = 2.34$, $p = .505$], and

reaction time variability [$\chi^2(3) = 1.37$, $p = .712$].

Effects of autistic and alexithymic traits on cue effect variables

Next, NLME models (AQ-50, TAS-20, and its interaction term) were performed to assess the effect of individual differences on the cue effect variables. Statistical results are shown in Table 5.6.

Table 5.6: Results of the cue effect NLME models fitted for (left) Study 1 (pain) and (right) Study 2.5 (vision). $\hat{\beta}$: the estimated beta coefficient; SE: standard error of $\hat{\beta}$; p-value: indicates whether a predictor variable significantly predicts the data or not. AIC, BIC, and Log-Likelihood indicate the model fit. * $p < .05$, ** $p < .01$, *** $p < .001$.

	Study 1 (pain)						**Study 2.5 (vision)**					
	$\hat{\beta}$	SE	p-value	AIC	BIC	Log-Likelihood	$\hat{\beta}$	SE	p-value	AIC	BIC	Log-Likelihood
Accuracy difference												
AQ-50	0.103	0.183	.577				1.17×10^{-2}	0.129	.928			
TAS-20	8.45×10^{-2}	8.85×10^{-2}	.343	433.72	446.95	-210.86	5.93×10^{-2}	8.25×10^{-2}	.474	779.16	796.45	-383.58
AQ-50 × TAS-20 interaction	-2.61×10^{-3}	3.11×10^{-3}	.405				-2.99×10^{-5}	2.35×10^{-3}	.990			
Mean reaction time difference												
AQ-50	3.66	3.30	.272				2.15	0.994	.032*			
TAS-20	1.83	1.68	.280	873.84	887.42	-430.92	1.20	0.619	.055	1369.86	1387.34	-678.93
AQ-50 × TAS-20 interaction	-4.59×10^{-2}	5.71×10^{-2}	.425				-2.91×10^{-2}	1.78×10^{-2}	.104			
Reaction time variability difference												
AQ-50	-0.129	4.94	.979				0.456	0.995	.647			
TAS-20	-1.66	2.51	.511	905.12	918.52	-446.56	0.396	0.619	.523	1447.17	1464.91	-717.59
AQ-50 × TAS-20 interaction	3.17×10^{-2}	8.52×10^{-2}	.711				-8.35×10^{-3}	1.81×10^{-2}	.645			

Study 1 (pain) None of the terms were found to be significant in Study 1.

Study 2.5 (vision) The cue effect (difference between the 80/20 and 50/50 dark conditions), as measured by mean reaction time, was significantly predicted by autistic traits, but not alexithymic traits. However, unexpectedly, the cue effect was reversed, such that reaction times were slower in the 80/20 than 50/50 condition (as indicated by negative cue effect values shown in Figure 5.5): the lower the autistic traits, the greater the cue effect in the unexpected direction.

Simple correlations between self-report measures and cue effect variables

Study 1 (pain) Simple correlations between cue effect variables and self-report measures can be found in Table 5.7. As expected, many of the self-report questionnaire scores were correlated with one another. While the cue effect variables were correlated with one another, none of the self-report questionnaire measures were correlated with the cue effect variables. The accuracy cue effect was negatively correlated with the mean reaction time cue effect and the reaction time

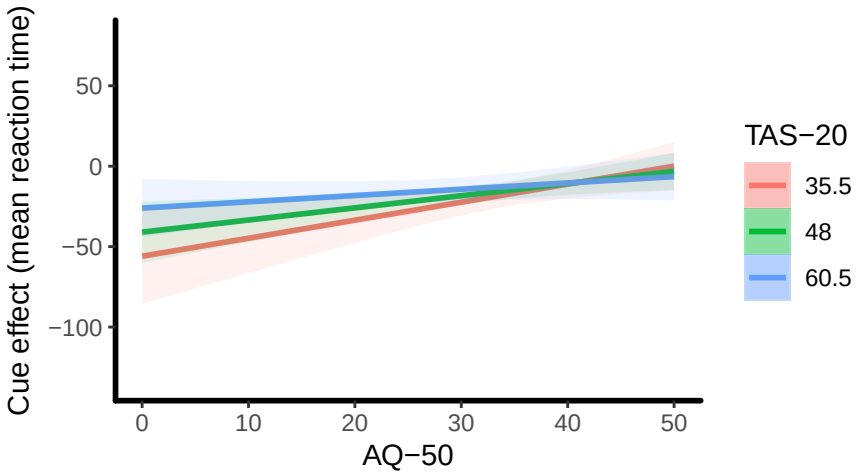


Figure 5.5: Relationship between AQ-50 and TAS-20, and cue effect variable (mean reaction time) for Study 2.5 (vision). Significant effect of autistic traits, but not alexithymic traits was found. Alexithymic scores are grouped into three categories according to the TAS-20 scores: low, medium, and high alexithymic traits. Shaded regions indicate the 95% confidence interval.

variability cue effect, where the greater the accuracy cue effect, the less the mean reaction time cue effect.

Table 5.7: Simple correlations between self-report measures and cue effect variables for Study 1 (pain). AQ-50: autistic traits, TAS-20: alexithymic traits, STAI-1: state anxiety, STAI-2: trait anxiety, BDI-II: depressive traits, PCS: pain catastrophising trait, BPQs-A: bodily awareness, IAS: interoceptive accuracy, IATS: interoceptive attention, IUS-12: intolerance of uncertainty, FSIQ: cognitive intelligence, and cue effect variables (accuracy, mean reaction time, and reaction time variability) calculated as the difference between the 80/20 and 50/50 high conditions. diff: difference, acc: accuracy, rt: reaction time, sd: variability. * $p < .05$, ** $p < .01$, *** $p < .001$.

	Age	AQ-50	TAS-20	STAI-1	STAI-2	BDI-II	PCS	BPQs-A	IAS	IATS	IUS-12	FSIQ	Acc diff	Mean rt diff
Age														
AQ-50	.531*													
TAS-20	.266	.808***												
STAI-1	.136	.502	.654**											
STAI-2	-.064	.539*	.786***	.741**										
BDI-II	-.106	.467	.667**	.750**	.920***									
PCS	.013	.379	.535*	.599*	.723**	.720**								
BPQs-A	-.257	-.025	.225	.568*	.639*	.673**	.706**							
IAS	-.208	-.837***	-.888***	-.735**	-.741**	-.689**	-.640*	-.330						
IATS	-.206	-.076	-.051	.244	.298	.440	.581*	.665**	-.064					
IUS-12	.103	.686**	.803***	.652**	.834***	.755**	.759**	.380	-.792***	.198				
FSIQ	.043	.251	.249	.022	.054	-.127	-.404	-.388	-.220	-.657**	-.061			
Acc diff	-.142	-.236	-.150	-.357	-.249	-.292	-.151	-.285	.182	-.387	-.124	.199		
Mean rt diff	.161	.197	.066	-.021	-.169	-.187	-.152	-.216	-.125	-.106	-.143	-.049	-.610*	
rt sd diff	.158	-.008	-.222	-.186	-.444	-.449	-.388	-.446	.154	-.190	-.370	.022	-.538*	.874***

Study 2.5 (vision) Simple correlations between cue effect variables and self-report measures can be found in Table 5.8. Similar to the Study 1 (pain) results, many of the self-report questionnaire scores were correlated with one another. Also, the cue effect variables were correlated with one another, but none of the self-report questionnaire measures were correlated with the cue effect variables. The greater the accuracy cue effect, the less the mean reaction

time and reaction time variability cue effect.

Table 5.8: Simple correlations between self-report measures and cue effect variables for Study 2.5 (vision). AQ-50: autistic traits, TAS-20: alexithymic traits, STAI-1: state anxiety, STAI-2: trait anxiety, BDI-II: depressive traits, PCS: pain catastrophising trait, IAS: interoceptive accuracy, IATS: interoceptive attention, IUS-12: intolerance of uncertainty, MR: matrix reasoning (T-score), and cue effect variables (accuracy, mean reaction time, and reaction time variability) calculated as the difference between 80/20 and 50/50 high conditions. diff: difference, acc: accuracy rt: reaction time, sd: variability. * $p < .05$, ** $p < .01$, *** $p < .001$.

	Age	AQ-50	TAS-20	STAI-1	STAI-2	BDI-II	PCS	IAS	IATS	IUS-12	MR	Acc diff	Mean rt diff
Age													
AQ-50	.138												
TAS-20	-.250	-.662**											
STAI-1	-.262	-.488	.757**										
STAI-2	-.334	-.596*	.887***	.888***									
BDI-II	-.265	-.668**	.871***	.823***	.969***								
PCS	-.450	-.526	.744**	.616*	.779**	.777**							
IAS	.131	.198	-.754**	-.607*	-.672**	-.594*	-.538*						
IATS	-.352	-.472	.519	.419	.538*	.591*	.566*	-.314					
IUS-12	-.345	-.725**	.903***	.736**	.889***	.884***	.861***	-.599*	.628*				
MR	.179	.231	-.216	-.266	-.248	-.348	-.438	-.201	-.430	-.355			
Acc diff	-.045	-.148	.212	-.008	.075	.144	.042	-.263	-.023	.084	.026		
Mean rt diff	.125	.256	-.248	-.106	-.299	-.347	-.252	.158	-.196	-.249	-.017	-.742**	
rt sd diff	.143	.039	-.163	-.031	-.236	-.254	-.167	.163	-.183	-.130	-.182	-.547*	.823***

Effects of self-report measures on the cue effect

Elastic net regressions were performed next to assess the effect of self-report measures on the cue effect (Table 5.9). None of the models showed non-zero coefficients for either Study 1 (pain) or Study 2.5 (vision).

Table 5.9: Results of the cue effect elastic net models with nuisance covariates for Studies 1 (pain) and 2.5 (vision). Dependent variables were cue effect variables (accuracy, mean reaction time, reaction time variability differences between the 80/20 and 50/50 high conditions). Statistics are based on the largest λ at which MSE is within 1 standard error of the smallest MSE. Measure: the loss used for cross-validation; SE: standard error; Non-zero variables: number, names and the corresponding coefficients of the non-zero coefficients. Independent variables entered into the models were: age, AQ-50, TAS-20, STAI-1, STAI-2, BDI-II, PCS, IAS, IATS, and IUS-12. Study 1 (pain) also had BPQs-A and FSIQ, and Study 2.5 (vision) had MR. Participant sample size differ depending on the variable, as statistical outliers were removed prior to analyses.

	Study 1 (pain)					**Study 2.5 (vision)**				
	N	λ	Measure	SE	Non-zero variables	N	λ	Measure	SE	Non-zero variables
Accuracy	71	0.122	0.537	0.102	0	113	7.04×10^{-2}	0.371	6.30×10^{-2}	0
Mean reaction time	75	0.201	0.882	0.102	0	115	8.84×10^{-2}	0.663	0.108	0
Reaction time variability	73	0.157	0.700	7.41×10^{-2}	0	121	8.88×10^{-2}	0.945	0.101	0

5.3.4 Condition and Group Differences in DDM Variables

Condition comparisons

First, the effect of condition (80/20 high, 50/50 high, 50/50 low) on three DDM variables (α, Z_r, V) was explored. Condition comparisons are illustrated in Figure 5.6. Mean values for each DDM variable per condition can be found in Table 5.10.

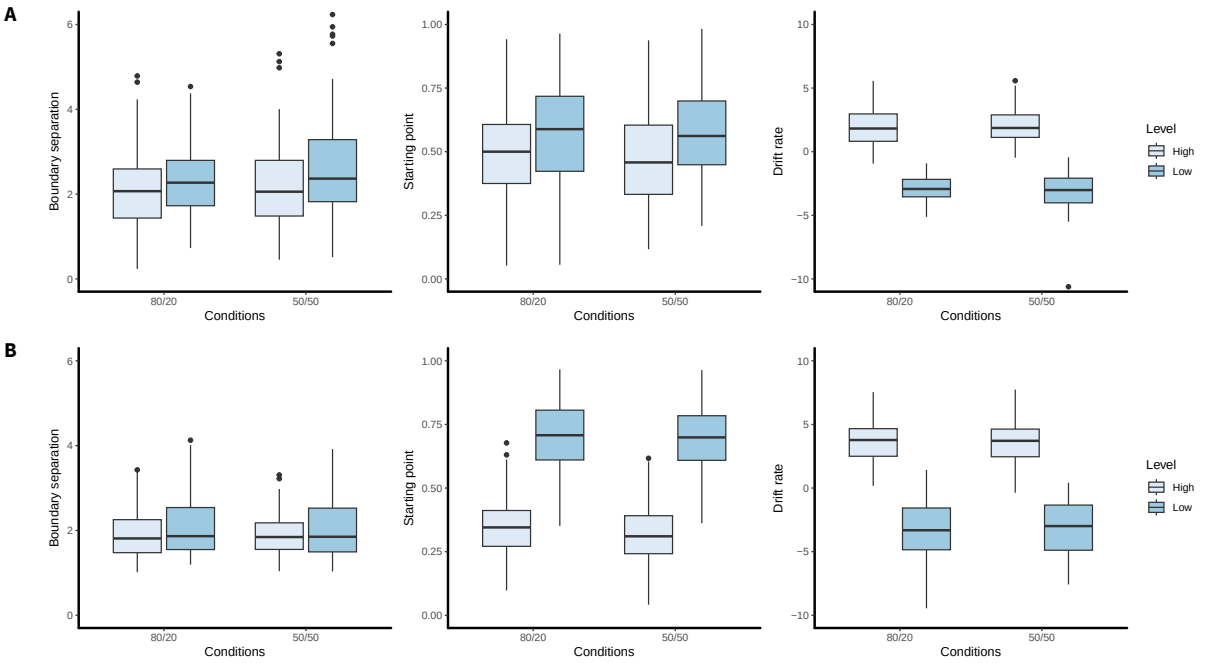


Figure 5.6: Comparisons of the DDM variables per condition for (A) Study 1 (pain) and (B) Study 2.5 (vision): (left) boundary separation, (middle) starting point, (right) drift rate. All variables were centred prior to analysis (log-transformed prior to centring where appropriate), with statistical outliers removed. Kruskal-Wallis test showed significant effect of condition for the drift rate and the starting point for both Studies 1 (pain) and 2.5 (vision). Study 1 (pain) also found significant difference between conditions for the boundary separation.

Study 1 (pain) Kruskal-Wallis test showed significant effects of condition for the boundary separation [$\chi^2(2) = 9.02$, $p = .010$], the starting point [$\chi^2(2) = 12.09$, $p = .002$], and the drift rate [$\chi^2(2) = 148.13$, $p < .001$].

The starting point was biased towards low pain for high than low pain in the 50/50 condition [$Z = -3.23$, $p = .004$], but no significant difference was found between the 80/20 and 50/50 high conditions [$Z = 0.489$, $p = 1.00$]. The drift rate was faster for the high than low 50/50 condition [$Z = 10.67$, $p < .001$], but no significant difference was found between the 80/20 and 50/50 high conditions [$Z = -0.261$, $p = 1.00$]. Pair-wise comparisons of the boundary separation found no

Table 5.10: Means of the DDM variables per condition for Studies 1 (pain) and 2.5 (vision). Participant sample size differ per variable, per condition, as statistical outliers were removed per variable, per condition. Sample size per group is shown for Study 1 (pain). Study 2.5 (vision) did not have a group structure.

		80/20 high			50/50 high			50/50 low			Difference (80/20 - 50/50 high)		
		N	Mean (SD)	Median [Min, Max]	*N*	Mean (SD)	Median [Min, Max]	*N*	Mean (SD)	Median [Min, Max]	*N*	Mean (SD)	Median [Min, Max]
Boundary separation													
Study 1 (pain)	aut+alex	15	1.91 (0.965)	2.07 [0.248, 3.67]	15	1.91 (1.01)	1.97 [0.452, 4.01]	15	2.48 (0.944)	2.41 [0.732, 4.00]	15	-2.55×10^{-3} (0.348)	-0.101 [-0.496, 0.912]
	aut-alex	11	1.77 (0.840)	1.78 [0.322, 3.16]	11	2.02 (0.775)	1.93 [0.873, 3.38]	11	2.07 (0.525)	1.98 [1.27, 3.28]	10	-0.113 (0.255)	-8.41×10^{-2} [-0.612, 0.281]
	alex	13	1.79 (0.866)	1.61 [0.702, 4.11]	13	1.96 (1.14)	1.80 [0.798, 5.12]	13	2.43 (1.34)	1.96 [1.16, 6.42]	13	-0.171 (0.454)	-9.75×10^{-2} [-1.01, 0.729]
	nt	34	2.32 (1.04)	2.28 [0.235, 4.79]	33	2.39 (1.05)	2.26 [0.544, 5.31]	34	3.07 (1.55)	2.80 [0.515, 6.23]	31	-0.185 (0.465)	-0.175 [-1.09, 0.774]
	Overall	73	2.06 (0.980)	2.07 [0.235, 4.79]	72	2.16 (1.02)	2.06 [0.452, 5.31]	73	2.68 (1.33)	2.37 [0.515, 6.42]	69	-0.132 (0.413)	-0.102 [-1.09, 0.912]
Study 2.5 (vision)		145	1.92 (0.530)	1.81 [1.02, 3.43]	144	1.91 (0.467)	1.84 [1.04, 3.31]	146	2.08 (0.688)	1.85 [1.03, 3.92]	130	1.38×10^{-3} (0.336)	-1.48×10^{-2} [-0.858, 0.880]
Starting point													
Study 1 (pain)	aut+alex	15	0.530 (0.208)	0.500 [0.250, 0.942]	15	0.475 (0.199)	0.450 [0.117, 0.894]	15	0.516 (0.163)	0.523 [0.208, 0.825]	15	5.49×10^{-2}(0.151)	6.36×10^{-2} [-0.221, 0.271]
	aut-alex	12	0.517 (0.160)	0.511 [0.260, 0.841]	12	0.526 (0.185)	0.507 [0.289, 0.938]	12	0.605 (0.172)	0.652 [0.258, 0.875]	11	3.73×10^{-2} (0.136)	2.42×10^{-2} [-0.182, 0.223]
	alex	13	0.560 (0.165)	0.591 [0.207, 0.911]	13	0.564 (0.159)	0.591 [0.245, 0.734]	13	0.493 (0.156)	0.536 [0.225, 0.803]	13	-3.92×10^{-3} (0.175)	-3.58×10^{-2}[-0.258, 0.375]
	nt	36	0.439 (0.193)	0.443 [5.24×10^{-2}, 0.888]	36	0.434 (0.173)	0.406 [0.191, 0.841]	36	0.628 (0.187)	0.596 [0.313, 0.983]	35	1.67×10^{-2} (0.137)	1.43×10^{-2} [-0.245, 0.257]
	Overall	76	0.490 (0.190)	0.500 [5.24×10^{-2}, 0.942]	76	0.479 (0.182)	0.458 [0.117, 0.938]	76	0.579 (0.181)	0.562 [0.208, 0.983]	74	2.39×10^{-2} (0.145)	8.05×10^{-3} [-0.258, 0.375]
Study 2.5 (vision)		145	0.344 (0.112)	0.345 [9.76×10^{-2}, 0.677]	145	0.325 (0.110)	0.310 [4.17×10^{-2}, 0.617]	148	0.700 (0.122)	0.699 [0.362, 0.964]	146	1.11×10^{-2} (0.111)	3.05×10^{-3} [-0.295, 0.316]
Drift rate													
Study 1 (pain)	aut+alex	15	2.05 (1.71)	1.88 [-0.936, 5.12]	15	2.46 (1.27)	2.43 [0.326, 5.20]	14	-2.61 (1.16)	-3.04 [-4.48, -0.439]	13	-7.48×10^{-2} (0.679)	-7.50×10^{-2} [-0.916, 1.39]
	aut-alex	12	2.26 (1.46)	1.96 [-0.0483, 4.80]	12	2.02 (1.38)	1.61 [0.318, 5.01]	12	-3.66 (2.42)	-2.84 [-10.6, -1.48]	11	-3.70×10^{-2} (0.655)	6.81×10^{-2} [-1.11, 0.861]
	alex	13	1.21 (1.17)	1.08 [-0.622, 3.29]	13	1.55 (1.20)	1.62 [-0.473, 4.39]	13	-3.10 (1.39)	-2.86 [-5.48, -0.965]	12	-0.136 (0.770)	-0.176 [-1.68, 1.31]
	nt	36	2.03 (1.43)	1.92 [-0.382, 5.57]	35	2.08 (1.51)	1.82 [-0.444, 5.58]	35	-3.23 (1.21)	-3.14 [-5.51, -0.790]	35	-8.96×10^{-2} (0.829)	-7.82×10^{-2} [-1.64, 1.99]
	Overall	76	1.93 (1.47)	1.82 [-0.936, 5.57]	75	2.05 (1.39)	1.86 [-0.473, 5.58]	74	-3.16 (1.49)	-3.02 [-10.6, -0.439]	71	-8.66×10^{-2} (0.754)	-7.50×10^{-2} [-1.68, 1.99]
Study 2.5 (vision)		147	3.67 (1.54)	3.78 [0.177, 7.54]	146	3.59 (1.58)	3.71 [-0.370, 7.74]	142	-3.20 (2.12)	-2.99 [-7.58, 0.415]	143	0.127 (1.05)	0.233 [-2.46, 2.99]

significant differences between either of the comparisons: between the 80/20 and 50/50 high conditions [Z = -0.417, p = 1.00], and between the high and low 50/50 conditions [Z = -2.36, p = .055].

Study 2.5 (vision) Kruskal-Wallis test showed a significant effect of condition for the starting point [$\chi^2(2) = 277.78$, $p < .001$], and the drift rate [$\chi^2(2) = 285.83$, $p < .001$], but not for the boundary separation [$\chi^2(2) = 2.49$, $p = .288$].

The starting point for the 50/50 dark condition was biased towards light image than the 50/50 light condition [Z = -14.94, $p < .001$], but no significant difference was found between the 80/20 and 50/50 dark conditions [Z = 1.12, p = .782]. The drift rate was faster for dark than light images in the 50/50 condition [Z = 14.53, $p < .001$], but no significant difference was found between the 80/20 and 50/50 high conditions [Z = 0.273, p = 1.00].

Group comparisons

For Study 1 (pain), group comparisons were also performed (aut+alex, aut-alex, alex, nt groups). Difference scores (difference in the three DDM variables between the 80/20 and 50/50 high conditions) were also compared. No significant effect of group was found for any of the variables across all comparisons (Table 5.11).

Table 5.11: Results of the group comparisons for DDM variables for Study 1 (pain) per condition (80/20 high, 50/50 high, 50/50 low), and the difference score between the 80/20 and 50/50 high conditions. None of the Kruskal-Wallis tests showed significant effect of group in any of the variables. * $p < .05$, ** $p < .01$, *** $p < .001$.

		80/20 high		50/50 high		50/50 low		Difference	
	df	χ^2	p-value	χ^2	p-value	χ^2	p-value	χ^2	p-value
Boundary separation (α)	3	4.90	.179	3.87	.275	4.57	.206	1.13	.769
Starting point (Z_r)	3	4.46	.216	6.69	.082	5.88	.117	2.13	.545
Drift rate (V)	3	3.18	.364	4.03	.258	1.24	.744	0.478	.924

5.3.5 Individual Differences in DDM variables

To conclude the analysis, elastic net regressions were performed to assess whether any of the self-report measures collected in the present study significantly predicted any of the DDM variables. For this analysis, any participants with incomplete questionnaire data (i.e., Study 2.5 (vision) participants who did not complete the optional IUS-12 and MR) were removed prior to performing the correlations and elastic net regressions.

Simple correlations between self-report measures and DDM variables

Simple correlations of all self-report measures that were used as independent variables in the elastic net analysis, and the DDM variables can be found in Table 5.12 for Study 1 (pain), and Table 5.13 for Study 2.5 (vision).

Study 1 (pain) IUS-12 was significantly negatively correlated with all of the DDM variables for the 80/20 high and 50/50 low conditions. It was also negatively correlated with starting point and drift rate for the 50/50 high condition. IUS-12 is highly positively correlated with AQ-50 (r = .800, $p < .001$), TAS-20 (r = .858, $p < .001$), STAI-1 (r = .720, $p < .001$), STAI-2 (r = .882, $p < .001$), BDI-II (r = .762, $p < .001$), and PCS (r = .735, $p < .001$), and negatively correlated with IAS (r = -.701, $p < .001$).

AQ-50 and TAS-20 were significantly negatively correlated with the boundary threshold for all conditions, and the starting point for the 50/50 low condition. AQ-50 and TAS-20 were also significantly positively correlated with the starting point in the 80/20 condition, and the drift rate in the 50/50 low condition. TAS-20 was also negatively correlated with the drift rate for the

80/20 high condition, and positively correlated with the drift rate for the 50/50 low condition and boundary separation difference.

Study 2.5 (vision) There were only a limited number of significant correlations between self-report measures and the DDM variables, mostly found in the 80/20 dark condition. Trait anxiety (STAI-2) and depressive traits (BDI-II) were negatively correlated with the boundary separation and the drift rate, but positively correlated with the starting point for the 80/20 dark condition. BDI-II was also negatively correlated with the drift rate for the 50/50 dark condition. MR was negatively correlated with the 80/20 dark boundary separation, but positively correlated with the starting point and the drift rate. IATS was negatively correlated with the drift rate difference. Unlike Study 1 (pain), AQ-50 and TAS-20 were not significantly correlated with any of the DDM variables.

Table 5.12: Simple correlations between self-report measures and DDM variables for Study 1 (pain). AQ-50: autistic traits, TAS-20: alexithymic traits, STAI-1: state anxiety, STAI-2: trait anxiety, BDI-II: depressive traits, PCS: pain catastrophising trait, BPQs-A: bodily awareness, IAS: interoceptive accuracy, IATS: interoceptive attention, IUS-12: intolerance of uncertainty, FSIQ: cognitive intelligence, and variables computed from the DDM per condition (80/20 high, 50/50 high, 50/50 low, difference between 80/20 and 50/50 high). α: boundary separation, Z_r: starting point, and V: drift rate. All variables are log-transformed (where appropriate) and centred. * $p < .05$, ** $p < .01$, *** $p < .001$.

														80/20 high			50/50 high			50/50 low			Difference	
		Age	AQ-50	TAS-20	STAI-1	STAI-2	BDI-II	PCS	BPQs-A	IAS	IATS	IUS-12	FSIQ	α	Z_r	V	α	Z_r	V	α	Z_r	V	α	Z_r
	age																							
	AQ-50	.644***																						
	TAS-20	.466*	.864***																					
	STAI-1	.328	.604**	.723***																				
	STAI-2	.272	.696***	.842***	.805***																			
	BDI-II	.141	.574**	.706***	.817***	.900***																		
	PC	.198	.474*	.586**	.678***	.723***	.766***																	
	BPQs-A	-.066	.091	.280	.597**	.598**	.675***	.740***																
	IAS	-.241	-.755***	-.795***	-.676***	-.639***	-.644***	-.631***	-.338															
	IATS	-.095	-.031	.016	.310	.277	.466*	.632***	.690***	-.090														
	IUS-12	.364	.800***	.858***	.720***	.882***	.762***	.735***	.398	-.701***	.190													
	FSIQ	.199	.391	.362	.178	.268	.042	-.261	-.285	-.222	-.566**	.157												
	α	-.464*	-.617**	-.566**	-.298	-.549**	-.273	-.094	.068	.168	.281	-.632***	-.469*											
80/20 high	Z_r	.447*	.447*	.476*	.247	.422*	.190	.091	.103	-.173	-.104	.443*	.283	-.725***										
	V	-.304	-.355	-.462*	-.312	-.392	-.316	-.378	-.322	.266	-.233	-.446*	.064	.359	-.764***									
	α	-.417*	-.581**	-.556**	-.242	-.498*	-.198	-.063	.057	.191	.315	-.583**	-.437*	.955***	-.756***	.401								
50/50 high	Z_r	.478*	.363	.389	.390	.417*	.359	.191	.232	-.103	.175	.298	.216	-.433*	.685***	-.629**	-.315							
	V	-.285	-.268	-.351	-.307	-.308	-.341	-.385	-.288	.153	-.350	-.301	.130	.142	-.442*	.837***	.111	-.693***						
	α	-.469*	-.603**	-.564**	-.324	-.541**	-.281	-.118	-.009	.172	.237	-.609**	-.450*	.962***	-.785***	.517**	.944***	-.498*	.304					
50/50 low	Z_r	-.364	-.580**	-.625**	-.413*	-.583**	-.318	-.092	.053	.229	.260	-.620**	-.477*	.907***	-.675***	.350	.895***	-.369	.125	.884***				
	V	.255	.493*	.537**	.331	.349	.236	.216	-.044	-.285	-.061	.501*	.175	-.540**	.389	-.547**	-.567**	.225	-.492*	-.658***	-.667***			
	α	.322	.373	.433*	.020	.153	-.038	.057	-.092	-.245	-.234	.272	.078	-.401	.602**	-.642***	-.597**	.161	-.441*	-.504*	-.414*	.555**		
Difference (80/20-50/50 high)	Z_r	.150	.212	.201	-.123	.085	-.175	-.110	-.143	-.093	-.327	.248	.136	-.526**	.664***	-.383	-.683***	-.081	.116	-.530**	-.500*	.244	.648***	
	V	-.027	-.029	-.034	.063	-.001	.115	-.062	-.096	.106	-.053	-.163	.151	.177	-.413*	.253	.306	.199	-.263	.164	.182	-.005	-.270	-.786***

Table 5.13: Simple correlations between self-report measures and DDM variables for Study 2.5 (vision). AQ-50: autistic traits, TAS-20: alexithymic traits, STAI-1: state anxiety, STAI-2: trait anxiety, BDI-II: depressive traits, PCS: pain catastrophising trait, IAS: interoceptive accuracy, IATS: interoceptive attention, IUS-12: intolerance of uncertainty, MR: matrix reasoning (T-scored), and variables computed from the DDM per condition (80/20 dark, 50/50 dark, 50/50 light, difference between 80/20 and 50/50 dark). α: boundary separation, Z_r: starting point, and V: drift rate. All variables are log-transformed (where appropriate) and centred. * $p < .05$, ** $p < .01$, *** $p < .001$.

													80/20 dark			50/50 dark			50/50 light			Difference	
		Age	AQ-50	TAS-20	STAI-1	STAI-2	BDI-II	PCS	IAS	IATS	IUS-12	MR	α	Z_r	V	α	Z_r	V	α	Z_r	V	α	Z_r
	Age																						
	AQ-50	.126																					
	TAS20_total	-.168	-.587**																				
	STAI-1	-.187	-.427*	.806***																			
	STAI-2	-.289	-.512*	.894***	.911***																		
	BDI-II	-.241	-.587**	.863***	.851***	.969***																	
	PCS	-.405	-.497*	.775***	.654***	.801***	.796***																
	IAS	.054	.160	-.732***	-.621**	-.648***	-.553**	-.514*															
	IATS	-.319	-.438*	.543**	.438*	.543**	.570**	.587**	-.226														
	IUS-12	-.270	-.645***	.909***	.765***	.877***	.855***	.870***	-.586**	.650***													
	MR	.271	.256	-.231	-.279	-.315	-.417*	-.456*	-.159	-.403	-.344												
	α	.364	.076	-.362	-.403	-.529**	-.564**	-.410	.198	-.208	-.278	.375											
80/20 dark	Z_r	-.381	-.240	.259	.330	.415*	.483*	.357	-.144	.188	.309	-.543**	-.624**										
	V	.224	.163	-.343	-.407	-.516*	-.583**	-.365	.150	-.139	-.267	.421*	.925***	-.753***									
	α	.265	.146	-.260	-.254	-.352	-.458*	-.314	.196	-.017	-.184	.428*	.732***	-.757***	.792***								
50/50 dark	Z_r	-.175	-.120	.197	.230	.328	.391	.219	-.083	-.043	.097	-.375	-.787***	.630**	-.806***	-.649***							
	V	.059	.155	-.249	-.261	-.349	-.449*	-.220	.168	.113	-.112	.316	.748***	-.636**	.859***	.905***	-.786***						
	α	.397	.058	-.007	-.133	-.215	-.279	-.127	-.056	-.175	-.019	.357	.538**	-.625**	.584**	.646***	-.351	.527**					
50/50 light	Z_r	.150	.133	-.187	-.339	-.346	-.396	-.189	.119	-.116	-.147	.352	.390	-.581**	.505*	.614**	-.326	.543**	.789***				
	V	-.188	-.079	-.019	.111	.152	.216	.033	.047	.048	-.050	-.243	-.371	.480*	-.489*	-.567**	.267	-.525*	-.932***	-.872***			
	α	.017	-.254	.004	-.042	-.051	.043	-.038	-.127	-.178	.008	-.088	.236	.319	.041	-.461*	-.083	-.314	-.267	-.418*	.379		
Difference (80/20 - 50/50 dark)	Z_r	-.288	-.157	.132	.194	.194	.210	.209	-.115	.303	.286	-.256	.035	.548**	-.098	-.266	-.299	.025	-.442*	-.403	.354	.479*	
	V	.263	-.086	-.078	-.155	-.189	-.107	-.180	-.080	-.420*	-.201	.051	.181	-.081	.102	-.361	.116	-.411	.052	-.147	.105	.702***	-.220

Elastic net

Results of the elastic net regressions for Studies 1 (pain) and 2.5 (vision) can be found in Table 5.14. Most of the models found no non-zero coefficients, except for the boundary separation in the 80/20 high condition in Study 1 (pain).

Table 5.14: Results of the DDM elastic net models with nuisance covariates for Studies 1 (pain) and 2.5 (vision). Dependent variables were DDM variables (α, Z_r, V) per condition. Statistics are based on the largest λ at which MSE is within 1 standard error of the smallest MSE. Measure: the loss used for cross-validation; SE: standard error; Non-zero variables: number, names and the corresponding coefficients of the non-zero coefficients. Independent variables entered into the models were: age, AQ-50, TAS-20, STAI-1, STAI-2, BDI-II, PCS, IAS, IATS, and IUS-12. Study 1 also had BPQs-A and FSIQ, and Study 2 had MR. Participant sample size differ depending on the variable, as statistical outliers were removed prior to analyses.

	Study 1 (pain)							**Study 2.5 (vision)**						
Condition	N	λ	Measure	SE	Non-zero variables			N	λ	Measure	SE	Non-zero variables		
					N	Name	Coefficients					N	Name	Coefficients
Boundary separation (α)														
80/20 high	73	0.193	0.540	5.95×10^{-2}	1	IUS-12	-6.17×10^{-2}	119	0.211	0.734	6.35×10^{-2}	0		
50/50 high	72	0.208	0.546	6.06×10^{-2}	0			119	0.142	0.536	5.55×10^{-2}	0		
50/50 low	73	0.250	0.731	0.138	0			121	0.223	0.864	9.34×10^{-2}	0		
Difference	69	0.179	0.368	0.101	0			107	8.84×10^{-2}	0.302	5.62×10^{-2}	0		
Starting point (Z_r)														
80/20 high	76	0.199	1.02	0.105	0			120	0.223	0.722	5.99×10^{-2}	0		
50/50 high	76	0.262	1.01	0.152	0			121	0.132	0.790	0.126	0		
50/50 low	76	0.289	1.02	9.75×10^{-2}	0			123	0.147	1.11	6.90×10^{-2}	0		
Difference	74	0.159	0.820	8.76×10^{-2}	0			121	0.190	0.853	8.87×10^{-2}	0		
Drift rate (V)														
80/20 high	76	0.180	1.07	0.192	0			123	0.251	1.094	0.172	0		
50/50 high	75	0.199	0.9359	0.161	0			121	0.179	0.967	0.149	0		
50/50 low	73	0.157	0.4893	8.63×10^{-2}	0			117	5.65×10^{-2}	0.387	5.49×10^{-2}	0		
Difference	71	9.28×10^{-2}	0.5285	7.77×10^{-2}	0			119	0.128	0.698	7.71×10^{-2}	0		

Study 1 (pain) The only model with non-zero coefficients was the boundary separation for the 80/20 high condition, where IUS-12 was the only non-zero coefficient (-6.17×10^{-2}). This was a negative relationship, as illustrated in Figure 5.7, where the greater the intolerance of uncertainty, the narrower the boundary separation (i.e., less cautious decision-making).

Study 2 (vision) Non-zero coefficients were not found for any of the DDM variables across all conditions.

5.4 Discussion

The present study investigated whether probabilistic expectations about upcoming pain (or vision) modulate pain (or visual) perception analysed using DDM (boundary separation, starting

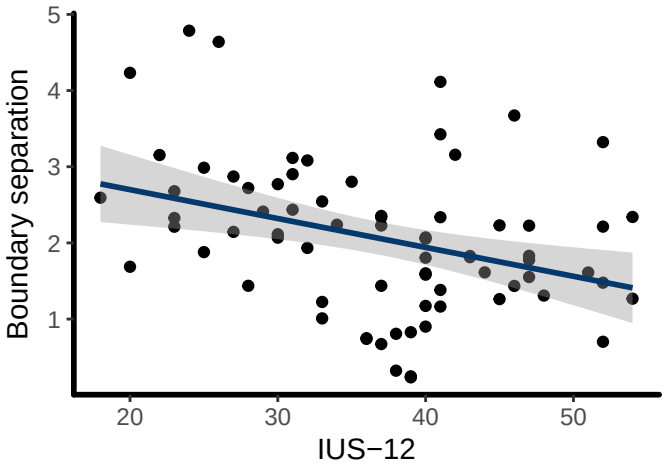


Figure 5.7: Relationship between IUS-12 and the boundary separation for the 80/20 high condition for Study 1. IUS-12 was the only non-zero coefficient found in all DDM elastic net models.

point, drift rate), and whether there are any effects of autism or alexithymia on the probabilistic cue effect. Studies were conducted using two different stimulus types (pain and vision) to assess whether the alexithymia hypothesis (Brewer et al., 2015) is limited to the interoceptive domain (pain), or whether it can also be observed in the exteroceptive domain (vision). Additionally, the study also aimed to see at whether any of the often highly correlated self-report measures were significant predictors of any of the DDM variables.

First, task performance (accuracy and reaction time) were analysed to assess the effect of condition and group. While the cue effect (difference between the 80/20 and 50/50 high conditions) was not observed in task accuracy for Study 1 (pain), it was in Study 2.5 (vision). The cue effect was seen in both studies in mean reaction time. The lack of a cue effect on accuracy in Study 1 (pain) is likely due to the ceiling effect observed in these data. While stimulation levels 2 and 8 were chosen as low and high pain based on a previous pain perception study (Wiech et al., 2014), it is possible that these two levels were too easily discriminated and therefore the task was not difficult enough. This is reflected in the fact that a large proportion of Study 1 (pain) participants (35.53%) were at ceiling across all conditions, whereas this was not the case for Study 2.5 (vision), as task difficulty was evaluated and adjusted through piloting (i.e., paradigm development studies, Studies 2.1-2.4).

Group and individual differences in the cue effect were also explored. In Study 1 (pain),

neither the group nor individual differences analyses found any significant effects. As the cue effect was only observed in mean reaction time, these results are likely due to the fact that the task was simply too easy, and the differences between conditions were too small, especially given the small sample size per group. For Study 2.5 (vision), however, NLME analysis found an effect of autistic traits, not alexithymic traits, on the cue effect as measured by the mean reaction time. Specifically, the lower the autistic traits, the faster the mean reaction time for the 50/50 than 80/20 high condition. However, this effect was not observed in an elastic net regression analysis with other self-report measures and is opposite to the predicted effect of the cue and so likely a false positive.

One of the advantages of DDM is the ability to estimate drift rates despite the accuracy ceiling effect, as long as some of the conditions have lower accuracy (Ratcliff, 2014). Therefore, DDM was used to compute boundary threshold, starting point, and drift rate per condition. There was an effect of condition for the starting point and the drift rate in both Studies 1 (pain) and 2.5 (vision), but no significant difference was found between the 80/20 and 50/50 high conditions. The results show that perceptual bias and processing speed were not significantly different for high conditions irrespective of the cue in both studies. When the probabilistic outcome of getting high or low stimuli was the same (50/50 cue), the starting point was smaller and the processing speed was faster for the high than low condition in both Studies 1 (pain) and 2.5 (vision). These results are in line with the other findings of greater drift rate, higher accuracy, and faster reaction time for high compared to low stimuli for the 50/50 conditions. Group comparisons of the DDM variables found no significant differences in any of the DDM variables across all conditions.

And finally, elastic net regressions were performed to assess individual differences in DDM variables. The only significant non-zero coefficient was found in the boundary separation for the 80/20 high condition in Study 1 (pain), where the results showed that the more intolerant to certainty (higher IUS-12), the smaller the boundary separation. The degree of intolerance of uncertainty (IUS-12) is highly positively correlated with autistic, alexithymic, anxious (state and trait), depressive and pain catastrophising traits, and negatively correlated with interoceptive accuracy. With heightened intolerance of uncertainty, defined as the tendency to find uncertain

situations aversive and anxiety provoking (Morriss & McSorley, 2019), it can be proposed that a "better safe than sorry" approach might be the optimal approach rather than sacrificing speed, especially in the context of pain, where the signals are more salient than visual stimuli. Moreover, with the use of probabilistic cues, the level of uncertainty was greater compared to deterministic cues, highlighting the role of intolerance of uncertainty in the perceptual process in this particular experimental context. Studies have found that incorporation of environmental uncertainty into perception is atypical in autistic people (Goris et al., 2018; Goris et al., 2021; Lawson et al., 2017; Sapey-Triomphe et al., 2022), which could be explained by the co-occurring intolerance of uncertainty.

In the present study, the main individual differences of interest were autistic and alexithymic traits. No autistic or alexithymic effect were observed in either Study 1 (pain) or Study 2.5 (vision). In contrast with previous literature (Iuculano et al., 2020; J. C. Kirchner et al., 2012; Manning et al., 2022; Pirrone et al., 2017), no effect of autism was found in the boundary separation. However, Pirrone et al. (2018) found no effect of autistic traits in the neurotypical population in DDM variables. The results from the present study may be due to the smaller sample size of autistic participants (n = 26) compared to the non-autistic participants (n = 47) used in the 50/50 low condition elastic net analysis.

The lack of an effect of autism on the starting position with the 80/20 cue, and on the cue effect itself, does not support the Bayesian account of autism (Pellicano & Burr, 2012). Under the Bayesian account of autism one would expect to see an atypical impact of prior expectations. The lack of an effect of alexithymia on the same parameters is also not consistent with the alexithymia hypothesis (Brewer et al., 2015), although it should be noted that this hypothesis states that *where seen*, effects of autism on interoceptive perception are actually effects of alexithymia. In these data, there were no effects of autism seen on the cue effect, so there is nothing to be explained by alexithymia.

One of the limitations of the study is that a ceiling effect was observed for many of the Study 1 (pain) participants, whereas paradigm development (Studies 2.1-2.4; vision) ensured that there were limited accuracy ceiling effects for Study 2.5 (vision). The comparisons of the results from the two studies should therefore be treated with caution, and future studies should use smaller

range of pain levels, such as levels 3 and 7, rather than levels and 2 and 8 to increase the task difficulty and thus to avoid the ceiling effect. While DDM is able to compute parameters even with the presence of a ceiling effect, there needs to be significant differences between conditions. This may have affected the results, especially given the small trial numbers for the 80/20 low condition (Study 1 (pain): 16 trials, Study 2.5 (vision): 30 trials). Given the issue with the ceiling effect, the study could be re-analysed using a hierarchical DDM, which requires fewer data points per participant compared to the traditional DDM as parameters are taken from a group distribution (Vandekerckhove et al., 2011).

Furthermore, setting a criteria of having accuracy of 80% or higher for practice trials for Study 2.5 (vision) may have eliminated greater variations in task performance. While this criterion was set due to concerns about data quality as the study was conducted online in the middle of the COVID-19 pandemic, there were significant proportions of participants (33.33% of total number of neurotypical Study 2.5 (vision) participants who either attempted or completed the task) who failed at the practice trial stage, despite having up to three attempts to meet the 80% threshold. These participants were therefore not allowed to continue to the main task. Either lowering the threshold, or adding alternative attention and bot check measures would have been more optimal.

Overall, the present study aimed to study the effect of expectation on the DDM variables, and how they are modulated by group and individual differences in autistic and alexithymic traits. The cue effect was limited, especially in Study 1 (pain). This affected the results, and condition differences (between 80/20 and 50/50 high) in the starting point was not found. No effect of autism or alexithymia was found, but intolerance of uncertainty, which is highly correlated with autistic and alexithymic traits, was the only non-zero coefficient in the boundary separation for the 80/20 high condition when pain stimuli was used. These studies do not support the Bayesian account of autism, nor the alexithymia hypothesis, perhaps because of the Study 1 (pain) ceiling effect and a reduced effect of probabilistic rather than deterministic cues, which would have resulted in less precise priors for all participants. Further research, with improvements in methodology, is needed to decipher the perceptual decision-making in pain and visual perception in autism and alexithymia.

Chapter 6

General Discussion

Pain is a salient and useful interoceptive signal, and the cognitive effects of pain modulation have been documented within the neurotypical population using the Bayesian framework. Pain perception has been found to be atypical in the autistic population, yet studies have found mixed results with most focusing on pain detection and thresholds, not cognitive modulation. In this thesis a series of experiments were conducted to test the cognitive modulation of pain, specifically, how expectation influences pain perception in autism. Given the findings that numerous mental health traits influence pain perception, as well as the heterogeneity within the autistic population, such as varying levels of alexithymia, individual differences in various mental health and personality traits were also accounted for, as an attempt to provide a clearer insight in the field of pain perception in autism research. Three theories that were investigated in this thesis were the cognitive modulation of pain perception (Wiech et al., 2008), the Bayesian account of autism (Pellicano & Burr, 2012), and the alexithymia hypothesis (Brewer et al., 2015).

6.1 Influence of Expectation on Pain Perception

The basis of this thesis was the hypothesis that manipulating expectation modulates pain perception. Expectation, presented in the form of a cue, was manipulated differently across three chapters to assess its effect on pain perception. In Chapters 3 and 4, cues had fixed values,

meaning the value for most cues did not change throughout the task, but there were some that were or became deceptive during the task without participants knowing. In Chapter 5, while the associations between cues and their related outcomes did not change, cues were probabilistic, rather than of fixed value.

Cue effects were observed across three chapters. The placebo manipulation (Chapter 3) resulted in reduced pain intensity rating (lower pain intensity rating for placebo trial compared to the control trial, despite both trials delivering the same stimulation level), and prediction error size and valence manipulation (Chapter 4) saw pain intensity ratings affected by cues (pain ratings were lower after seeing cue 2, rather than cue 8, despite both trials delivering the same stimulation level). However, the cue effect was limited when a probabilistic cue was used (Chapter 5). While a cue effect was observed both in accuracy and reaction time (higher accuracy and faster reaction time for cues that had greater bias for one of the outcomes) for the paradigm using visual stimuli, it was only observed in reaction time using the pain stimuli, and no cue effects were observed in any of the DDM variables.

These results add to the existing literature that expectation is an important cognitive modulator of pain perception (Wiech et al., 2008). Conditioning and verbal instructions are sufficient to create behavioural changes leading to statistically significant cue effects, where expectation, even in the presence of a prediction error, contributes to shaping perception. However, there are limits on how much expectation can influence pain perception, confirmed by the presence of a tipping point (Hird et al., 2019). The effect of a cue on perception was also confirmed in the visual domain, in line with the literature that general sensory perception can be understood within the Bayesian framework (Summerfield & de Lange, 2014).

6.1.1 Limitations

The lack of cue effect when using probabilistic cues within the pain domain (Study 1, Chapter 5) might be due to the differences in uncertainty related to the cue (i.e., probabilistic vs. deterministic). However, as a cue effect was observed in accuracy when using visual stimuli (Study 2.5, Chapter 5), the limited finding of cue effect in the pain paradigm is rather likely

due to the ceiling effect observed among many participants. While general comparison between the three chapters is warranted, direct comparisons should be performed with caution, due to differences in measurement of the cue effects.

The placebo hypoalgesia experiment (Chapter 3) and the prediction error size experiment (Chapter 4) quantified cue effects by calculating the difference in pain intensity ratings, whereas the probabilistic cueing experiment (Chapter 5) calculated accuracy and reaction time. Pain intensity ratings allow for a more fine-grained measurement of the cue effect, while it is less so for accuracy (a binary response of correct or incorrect). Accuracy, rather than pain intensity rating, was collected for modelling purposes (DDM). This limitation is mitigated by the measurement of reaction time, where a cue effect was found even in the pain paradigm of the probabilistic cueing task (Study 1, Chapter 5). Future studies therefore need to adjust the task difficulty for the pain version of the probabilistic cueing task (Study 1, Chapter 5), to first assess whether the lack of cueing effect observed in accuracy could at least partially be explained by the ceiling effect, or by the uncertainty in the cue.

6.1.2 Future Directions

In Chapter 5, where probabilistic cues were used, response caution was found to be modulated by intolerance of uncertainty when using pain stimuli (Study 1). Intolerance of uncertainty was not a significant predictor of the cue effect in the two experiments using fixed value cues (Chapters 3 and 4). Uncertainty is a broad term that encompasses multiple hierarchical levels, including sensory, state, rule, and outcome uncertainty (Bach & Dolan, 2012). Across all three chapters, outcome uncertainty was manipulated, as well as rule uncertainty for Chapters 3 and 4. Bach and Dolan (2012) state that outcome uncertainty is uncertainty about which of the possible next states will actually occur, whereas rule uncertainty is the uncertainty related to the transition rule between the present and the next state. For example, outcome uncertainty was the fact that it could not have been said that after seeing a circle, the stimulation level will definitely be high pain in the probabilistic cueing paradigm, as the circle cue was associated with 80% probability of high pain and 20% probability of low pain. An example of rule uncertainty was

when the rule that seeing a TENS-on cue will bring pain relief changed once in the placebo phase. Thus, even in this experiment, by manipulating expectations, some levels of uncertainty were introduced. The presence of an effect of intolerance of uncertainty in Chapter 5, but not in 3 and 4, may then be informative as to exactly which kind of uncertainty is picked up by the intolerance of uncertainty measure used in this thesis.

A possible next step would be to investigate the influence of expected and unexpected uncertainty, in an attempt to clarify the complex relation between expectation and uncertainty. A placebo hypoalgesia study by Au Yeung et al. (2014) which compared probabilistic reinforcement (expected uncertainty) and continuous reinforcement (no uncertainty) in the conditioning phase, showed that while the placebo effect was smaller in the probabilistic reinforcement paradigm than in the continuous reinforcement paradigm, the probabilistic reinforcement paradigm was resistant to extinction. It would be interesting to investigate how the placebo effect and extinction change when uncertainty is unexpected.

6.2 Influence of Autism on Cue Effects

This thesis also aimed to test the Bayesian account of autism (Pellicano & Burr, 2012) in the interoceptive domain, which had not been done previously. Individual differences in common mental health traits were taken into account across the three pain perception experiments (Chapters 3, 4, and 5), given the Chapter 2 results where heterogeneity in common mental health traits was found within the typical neurotypical participants in psychology experiments. It was thus important to account for common mental health and personality traits to control for individual differences across groups (aut+alex, aut-alex, alex, and nt), and also to ensure that any significant effects were due to variables of interest (autistic and alexithymic traits), rather than due to confounding variables (e.g., anxiety, depression, pain catastrophising).

To test the Bayesian account of autism, group and individual differences in autistic traits, as measured by the presence or absence of an autism diagnosis and AQ-50 scores, were considered across three chapters. For group comparisons, Chapters 3 and 5 had four-group structures (aut+alex, aut-alex, alex, and nt groups), whereas Chapter 4 had a two-by-two group structure

(autism and non-autism groups, and alexithymia and non-alexithymia groups). Individual differences in autistic traits were treated the same across all three chapters by using AQ-50 total scores.

Group comparisons across three chapters do not offer a clear story on the influence of autism on cue effects. How the cue effect changed over trials (i.e., the extinction function; Chapter 3) was the most complex in the aut+alex group compared to other groups (aut-alex, alex, and nt groups) in the placebo hypoalgesia experiment. However, these results point not only to the effect of autism, but also to the alexithymia effect (see Section 6.3). No autism group effects were found in both the prediction error size experiment (Chapter 4) and the probabilistic cueing experiment (Chapter 5).

When considering individual differences in autistic traits, using continuous AQ-50 scores rather than discrete groups, the story was still unclear. In the prediction error size experiment (Chapter 4), the cue effect was driven by autistic traits, where the higher the autistic traits, the lesser the cue effect, in line with the Bayesian account of autism. However, no effect of autistic traits on the cue effect was found in the placebo hypoalgesia experiment (Chapter 3). Yet, how the cue effect changed over time (i.e., the extinction function) was influenced by the interaction between autistic and alexithymic traits, where the higher both the scores, the more complex the changes in cue effect over the course of trials. No effect of autistic traits was found in the probabilistic cueing experiment (Chapter 5).

The results do not offer a consistent story on the effects of autism on the influence of expectation on pain perception, and therefore do not unambiguously support nor challenge the Bayesian account of autism. This is in line with the existing literature, where mixed results have been found (Cannon et al., 2021). These mixed results may be due to the fact that as outlined in Section 6.1.2, manipulating expectation also unintentionally manipulates uncertainty. Lawson et al. (2017) found that autistic adults overestimate environmental volatility (rule and outcome uncertainty), and in line with their findings, Goris et al. (2018) found that autistic adults showed less context-dependent modulation of sensory prediction errors, suggesting that incorporating rule and outcome uncertainty may be atypical in autistic individuals. Nonetheless, Manning et al. (2017)'s paradigm which involved reward conditions found intact estimation of environmental

volatility in autistic children. Future studies could investigate the effect of autism on rule and outcome uncertainty separately, and how it may differ at various stages of development.

6.2.1 Limitations

Across all studies, no cut-off score was set for AQ-50 for any of the participants. Participants were recruited and categorised into appropriate groups depending on the presence or absence of an autism diagnosis. This decision was made to ensure that participants across all the spectrum of AQ-50 scores were recruited, and also because AQ-50 scores were found to be inadequate predictors of autism diagnosis (Ashwood et al., 2016). Although there were significant group differences in autistic traits between the autism and non-autism groups across all studies, there were overlaps in AQ-50 scores between the two groups, likely explaining why significant effects of autism group were limited. Removing nt participants (categorised as such due to the absence of an autism diagnosis) based on high AQ-50 scores further narrows the pool of potential participants. From a practical aspect, recruitment for pain perception studies is difficult already. Adding an extra exclusion criterion to an already quite limiting exclusion criteria for nt participants (e.g., no current or psychiatric diagnoses or prescription of psychotropic medications) would make the recruitment process even more challenging. And given the findings from Chapter 2, it is likely more meaningful to use total questionnaire scores, rather than categorising participants into groups, given the great individual differences within each group. Thus, rather than conducting group comparisons, group structures could be used just for recruitment purposes.

Moreover, autistic people who participated in the pain perception studies are representative of only a small spectrum of the autistic population. Autism is a highly heterogeneous condition, with wide ranges in cognitive abilities and sensory sensitivities. To participate in the studies in this thesis, participants were required to at least be verbal and be able to give consent, understand the instructions and respond appropriately according to the task instructions, be able to withstand having various electrodes being stuck on their skin, be able to sit still for 30 to 40 minutes, and have pain tolerance within the mechanical limitations of the Digitimer DS7A device, which

delivered the electrical pulses. There were some participants who were unable to take part as they found the electrical stimulations incredibly painful, or did not feel the stimulation at the maximum possible level. Conducting pain perception studies already limits the participant pool, especially in the clinical population, and these requirements narrow the potential participant pool even further. The findings of this thesis, while they contribute to the autism research on pain perception, apply to a small group of people within the autistic population. This limitation is not specific to this thesis, but is an issue that needs to be considered generally in autism research. However, given the limited number of studies on pain perception in autism, especially those on cognitive modulation of pain in autism, this thesis presents a first step in better understanding autistic pain perception from a cognitive perspective.

6.2.2 Future Directions

Given that the studies in this thesis were somewhat restrictive in participant inclusion criteria, it would be interesting to assess differences in pain perception without cognitive modulation within the autistic population. What participants understand to be level 8 out of 10 pain, for example, likely differs between participants, especially within the autistic population. What is understood to be a clinical pain level (e.g., when I broke both my arms, I rated it as 8 out 10 pain level when the A&E doctor asked me), differs from research pain level (e.g., level 8 out 10 pain level is described as "definitely uncomfortable, but tolerable") for ethical reasons, but this is an implicit understanding at least among neurotypical participants, that may not be the case among the autistic participants. This is in addition to the findings showing differences in pain reporting in autistic people compared to non-autistic people (Kalingel-Levi et al., 2022; Nader et al., 2004). It is therefore necessary to assess what participants understand level 8 out of 10, for example, to be. In addition to collecting pain intensity ratings and any description of what that pain level feels like, it would be useful to also collect physiological measures, such as GSR and heart-rate variability, as well as pain history (e.g., history of self-harm, are they often in an environment where pain is common) to be used together to create a more comprehensive pain rating measure.

6.3 Alexithymia Hypothesis in Pain Perception

The third and final aim of the thesis was to test the alexithymia hypothesis (Brewer et al., 2015) using pain, which had never been done before. As when testing the effects of autism, group and individual differences in alexithymia were considered across three studies. For group comparisons, Chapters 3 and 5 had four-group structures (aut+alex, aut-alex, alex, and nt groups), whereas Chapter 4 had a two-by-two group structure (autism and non-autism groups, and alexithymia and non-alexithymia groups). Individual differences in alexithymic traits were treated the same across all three chapters by using TAS-20 total scores.

Effects of alexithymia were found within the autism group in Chapter 3, where the cue effect produced by the placebo hypoalgesia manipulation and how that cue effect changed over the course of the task, was greater in the aut+alex than the aut-alex group. An effect of alexithymia group was observed in the effect of prediction error valence, when the magnitude of the prediction error was large (Chapter 4). However, no effect of alexithymia group was found in the probabilistic cueing experiment (Chapter 5).

When treating alexithymic traits as a continuous variable and looking at individual differences in alexithymic traits, results support the alexithymia hypothesis. A quadratic relationship between the magnitude of the cue effect and alexithymic traits, and a quadratic relationship between how this cue effect changes over trials and the interaction between autistic and alexithymic traits, was found (Chapter 3). Moreover, the tipping point, and how it changes across trials were modulated by alexithymic traits (Chapter 4). These results converge to suggest that it is mostly alexithymic traits, rather than autistic traits, that modulate the cue effect and how it changes over time in pain perception, in support of the alexithymia hypothesis.

In applying the alexithymia hypothesis to the Bayesian account of autism, it was hypothesised that cue effects would be seen as weaker among alexithymic participants. Contrary to this hypothesis, cue effects were the greatest among highly alexithymic participants at the beginning of the task (Chapters 3 and 4). However, how the cue effect changed across trials was modulated by alexithymic traits, and the cue effect was smaller for high alexithymic participants at the end of the task. This means that the cue effect dissipated for high alexithymic participants as

they underwent further conditioning in the form of trials. This suggests that there may be a temporally-specific aspect to the cue effect, modulated by alexithymic traits.

6.3.1 Limitations

The alexithymia hypothesis suggests that that interoceptive difficulties observed in autism are due to the co-occurring alexithymia, rather than autism itself (Brewer et al., 2015). Thus, in the absence of an autism effect, the alexithymia hypothesis could not be applied. When testing whether the alexithymia hypothesis was limited to the interoceptive domain (Chapter 5), no effect of autism and alexithymia were observed in both pain stimuli and visual stimuli versions (Chapter 5). Thus, the results do not disprove the alexithymia hypothesis, and do not confirm whether or not it is limited to the interoceptive domain. Again, the pain version of the study needs to be repeated to assess whether the limited cue effect was due to the ceiling effect, so the two studies can be compared.

The effects of autistic and alexithymic traits were also tested while controlling for highly correlated covariates (i.e., elastic net regression analysis, Chapter 4). In doing so, the alexithymia effect disappeared, suggesting that the variance in how expectation influences pain perception is not best explained by autistic and alexithymic traits, when many covariates are considered. However, this may be due to limited statistical power, rather than evidence suggesting that there is no effect of alexithymia. One of the solutions to overcome this is to conduct large-scale collaborative consortia studies to increase the reliability of findings, while ensuring that data collection methods are standardised (Button et al., 2013). However, it should be considered that cultural differences in alexithymia levels may be explained by culturally based differences in the values of emotions, introducing further confounding variables that need to be controlled for (Dere et al., 2012).

Of note is the fact that two alexithymic participants who took part in earlier experiments of the thesis (Chapter 3) who were later invited back to participate in further studies (Chapters 4, 5) had a change in their autism diagnosis. They were initially categorised as alex participants, who were then recategorised as aut+alex participants. While autism and alexithymia are distinct

conditions (Cuve et al., 2022), the high correlation between autism and alexithymia cannot be ignored. These potential changes in group membership further support the use of questionnaire scores rather than groups to assess the effects of autism and alexithymia, but also raise the question of whether high autistic traits observed in some alexithymic participants is due to undiagnosed autism.

6.3.2 Future Directions

The change in the magnitude of the cue effect across trials, driven by alexithymic traits, is of great interest. This change in cue effect over time could be explained by the perceptual paradox, coined by Press et al. (2020). The perceptual paradox highlights that the Bayesian account of perception and cancellation theory co-exist, which claim that sensory evidence is enhanced by an expectation which matches it (Bayesian account), unless the unexpected event is considered to be significant (cancellation theory), and that which of these occurs is a temporally-sensitive process (Press et al., 2020). The perceptual paradox is relevant to the future directions from Section 6.1.2, where an investigation on expected and unexpected uncertainty, using a temporally-sensitive paradigm may provide an insight into how uncertainty is incorporated into perception over time, and how this process may be modulated by alexithymic traits. Nonetheless, an EEG experiment, for example, that would allow an investigation into the perceptual paradox, would require hundreds of trials, meaning hundreds of electrical stimulations. Ethical considerations therefore need to be taken into account.

6.4 General Considerations

6.4.1 Limitations

While it was beyond the scope of this thesis, the role of attention on pain perception cannot be disregarded. Expectation violation has a similar effect on pain processing as top-down attention, whereby unexpected and attended pain both increase the amplitude of event-related potentials (Fardo et al., 2017). Attention is especially relevant in the context of autism, where there is

high co-morbidity of ADHD (see Section A.2.1; Khachadourian et al., 2023). The experimental paradigms in this thesis require participants to repeatedly perform multiple tasks within short intervals of time, over a period of 20 to 40 minutes. Participants are asked to sit still in front of a computer screen, follow and remember the instructions, perceive the stimulation, and use the mouse or keyboard to indicate a response. There is a heavy cognitive load while performing the task, which may be modulated by the ability to appropriately attend to the task at hand (e.g., co-occurring ADHD). Moreover, autistic individuals are reported to have slower habituation and attentional biases against novelty, when the stimuli are complex (Arora et al., 2022; Vivanti et al., 2018), further complicating the matter. While self-time breaks were offered within the tasks to mitigate this limitation, it is necessary to acknowledge that the tasks were difficult and cognitively demanding.

Finally, the phenomenon of sensory fluctuations should be considered. Categorising individuals as either hypo or hypersensitive to pain based on one experimental session is likely not reflective of the individual's general pain experience. The results from this thesis, therefore, could only be interpreted as being a amalgamation of various factors that shaped that experimental session, such as individual's physical and mental conditions, environmental factors, and experimental manipulation. This is especially the case as MacLennan et al. (2022) showed that a majority of autistic individuals identify as experiencing a combination of sensory hypo/hyperreactivity, and sensory seeking, demonstrating the complexity of sensory experience within the autistic population. To obtain a more comprehensive view of participants' sensory profiles would require a longitudinal study.

6.4.2 Future Directions

In addition to the proposed research outlined in Sections 6.1.2, 6.2.2, 6.3.2, a common assumption made in pain perception experiments needs to be considered. The assumption, which underlies the experiments conducted for this thesis and most pain studies is that people can distinguish and report different levels of pain (Hird et al., 2019; Hoskin et al., 2019), and that it is useful to be able to do so. The further assumption is that a common scale can meaningfully

be used for clinical groups and the general population alike. However, it is plausible that while autistic people do recognise pain, their pain perception, modulated by individuals' alexithymic traits, have lower granularity when compared to neurotypical people. If the functionality of pain is simply to alert for potential tissue damage, it seems high pain granularity would be unnecessary. But it has other functions including emotional experience (Raja et al., 2020). Thus, having low pain granularity may have consequences in social interactions and communications which are known to be modulated by emotional experience, such as empathy (Coll et al., 2017).

Looking at pain granularity is different to the future directions outlined in Section 6.2.2, which is to obtain a more comprehensive view and compare pain experience in autistic and non-autistic people. This, on the other hand, is to look at pain granularity, the ability to distinguish between pain levels 3 and 4 out of 10, for example. There may be differences in discrimination reliability, where different pain reporting observed in autistic and alexithymic participants may be due to the discrepancy between physiological (measured by, e.g., heart-rate variability and pupil dilation; Haspert et al., 2020) and cognitive processing of pain (measured by, e.g., facial expressions; Nader et al., 2004). If there is a top-down dysregulation of sensory perception in autism, their basic physiological responses may be a more accurate predictor of pain stimulus intensity than their cognitive response. The predictive usefulness of basic physiological and behavioural responses may be dependent on pain stimulus intensity, with mixed responses at intermediate levels.

6.5 Concluding Remarks

This thesis aimed to investigate the effects of expectation in autism and alexithymia. The studies were successful in showing the effect of expectation on pain perception. However, results were inconclusive on the modulation of expectation on pain perception by autistic traits, further contributing to the mixed results regarding the Bayesian account of autism, but this time in the pain domain. However, the alexithymia hypothesis was supported across two studies, where it was mostly alexithymic traits, rather than autistic traits, that explained how expectation shaped pain perception. These were the first studies to investigate the alexithymia hypothesis

using pain, and add to the literature that alexithymia hypothesis can be applied in another type of interoceptive stimuli, pain. Together, these findings attempt to shed light on atypical pain perception observed in autism, and suggest that its atypicality could be explained by the differences in cognitive modulation and alexithymic traits. Pain cannot be simplified to just being a signal that notifies of potential tissue damage, and great variability observed in pain experience makes further studies necessary for better clinical interventions.

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Appendix A

Supplementary Materials

A.1 Chapter 2 Supplementary Materials

A.1.1 Results

Imputed data comparisons

T-tests were performed to determine whether statistical properties of Study 1 data sets were preserved pre- and post-imputation. As shown in Table A.1, t-tests demonstrated no significant differences between pre- and post-imputation data sets. Further, normalised root mean squared error (NRMSE) is indicative of residual variance for a model, whereby a lower value indicates less unexplained variance. In all of the imputed data sets, NRMSE value was close to 0.

Table A.1: Summary of t-statistics pre- and post-imputation, and normalized root mean squared error (NRMSE). Lower NRMSE values indicate less residual variance for a model.

Data set	Questionnaire	Range		NRMSE
		t-statistic	*p*-value	
EQoLS	WHO-5	[0.003, 0.029]	[.943, .997]	2.55×10^{-5}
EHIS	PHQ-8	[-0.063, 0.017]	[.893, .998]	1.40×10^{-4}
HSE 2016	GHQ-12	[-0.101, 0.034]	[.920, .995]	2.89×10^{-4}
HSE 2016	WEMWBS	[-0.012, 0.041]	[.964, .999]	4.31×10^{-4}
HSE 2018	GHQ-12	[-0.028, 0.038]	[.970, .999]	2.72×10^{-4}
HSE 2019	WEMWBS	[-0.010, 0.079]	[.937, .999]	4.45×10^{-4}
Study 2	WEMWBS-7	[-0.006, 0.008]	[.993, 1.000]	6.73×10^{-5}

Questionnaire category comparisons

BDI-II data were taken from Study 3, which categorised 63.97% as minimal, 17.81% as mild, 13.16% as moderate, and 5.06% as severe.

STAI-1 data were taken from Study 3, which categorised 53.24% as non-clinical level of anxiety, and 46.76% as clinically diagnosable level of anxiety. STAI-2 data were taken from Study 3, which categorised 33.20% as non-clinical level of anxiety, and 66.80% as clinically diagnosable level of anxiety. It should be noted that STAI was created without cut-offs, but a score of 40 is used to identify clinical level of anxiety, despite some recent criticism that the cut-off is overly inclusive (Womble et al., 2021).

DASS-21 data were taken from Study 3. For the depression sub-scale, participants were categorised as follows: 48.99% normal, 12.55% mild, 20.45% moderate, 8.50% severe, and 9.51% extremely severe. For the anxiety sub-scale, participants were categorised as follows: 60.73% normal, 5.47% mild, 15.99% moderate, 6.88% severe, and 10.93% extremely severe. For the stress sub-scale, participants were categorised as follows: 61.74% normal, 9.92% mild, 14.98% moderate, 9.72% severe, and 3.64% extremely severe.

GHQ-12 data were taken from HSE-2016, HSE-2018, and Study 3. HSE-2016 categorised 77.94% as none, 11.97% as mild, 7.93% as moderate, and 2.16% as severe. HSE-2018 categorised 81.55% as none, 10.41% as mild, 6.13% as moderate, and 1.91% as severe. Study 3 categorised 42.31% as none, 17.41% as mild, 21.66% as moderate, and 18.62% as severe.

PHQ-8 data were taken from EHIS and Study 3. EHIS categorised 91.49% as none, 6.99% as mild, 1.20% as moderate, 0.26% moderately severe, and 0.06% extremely severe. Study 3 categorised 26.32% as none, 27.13% as mild, 30.16% as moderate, 11.94% moderately severe, and 4.45% extremely severe.

WEMWBS data were taken from HSE-2016, HSE-2019 and Study 3, and WEMWBS-7 data were taken from Study 2. HSE-2016 categorised 6.99% as probable depression, 10.37% as possible depression, 71.38% as average well-being, and 11.26% as high mental well-being. HSE-2019 categorised 6.12% as probable depression, 7.73% as possible depression, 66.18% as average well-being, and 19.97% as high mental well-being. Study 2 categorised 5.55% as

probable depression, 24.23% as possible depression, 60.50% as average well-being, and 9.72% as high mental well-being. Study 3 categorised 40.28% as probable depression, 11.13% as possible depression, 41.30% as average well-being, and 7.29% as high mental well-being.

WHO-5 data were taken from EQoLS and Study 3. EQoLS had 73.23% categorised as well and 26.77% as poor well-being, compared to Study 3 which had 44.33% as well and 55.67% as poor well-being.

Figure A.1 shows effect sizes with the 95% confidence intervals for single chi-squared test comparisons between studies.

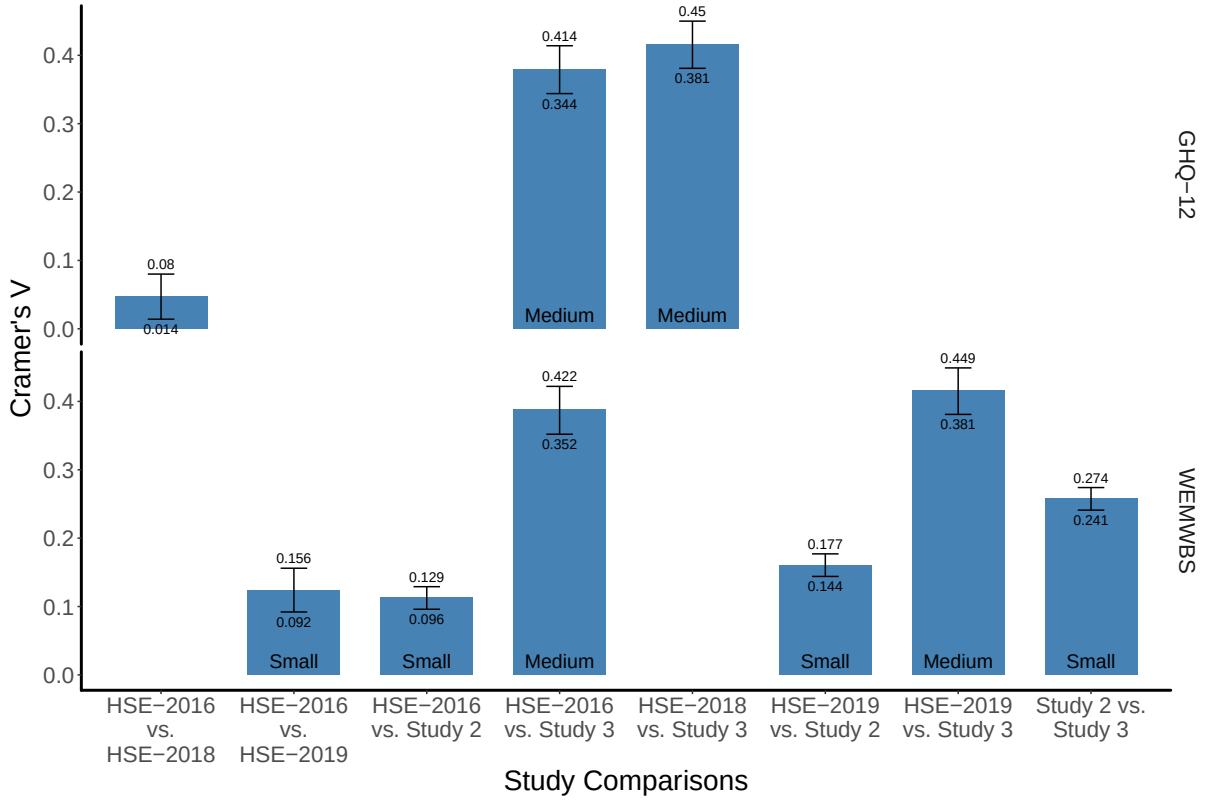


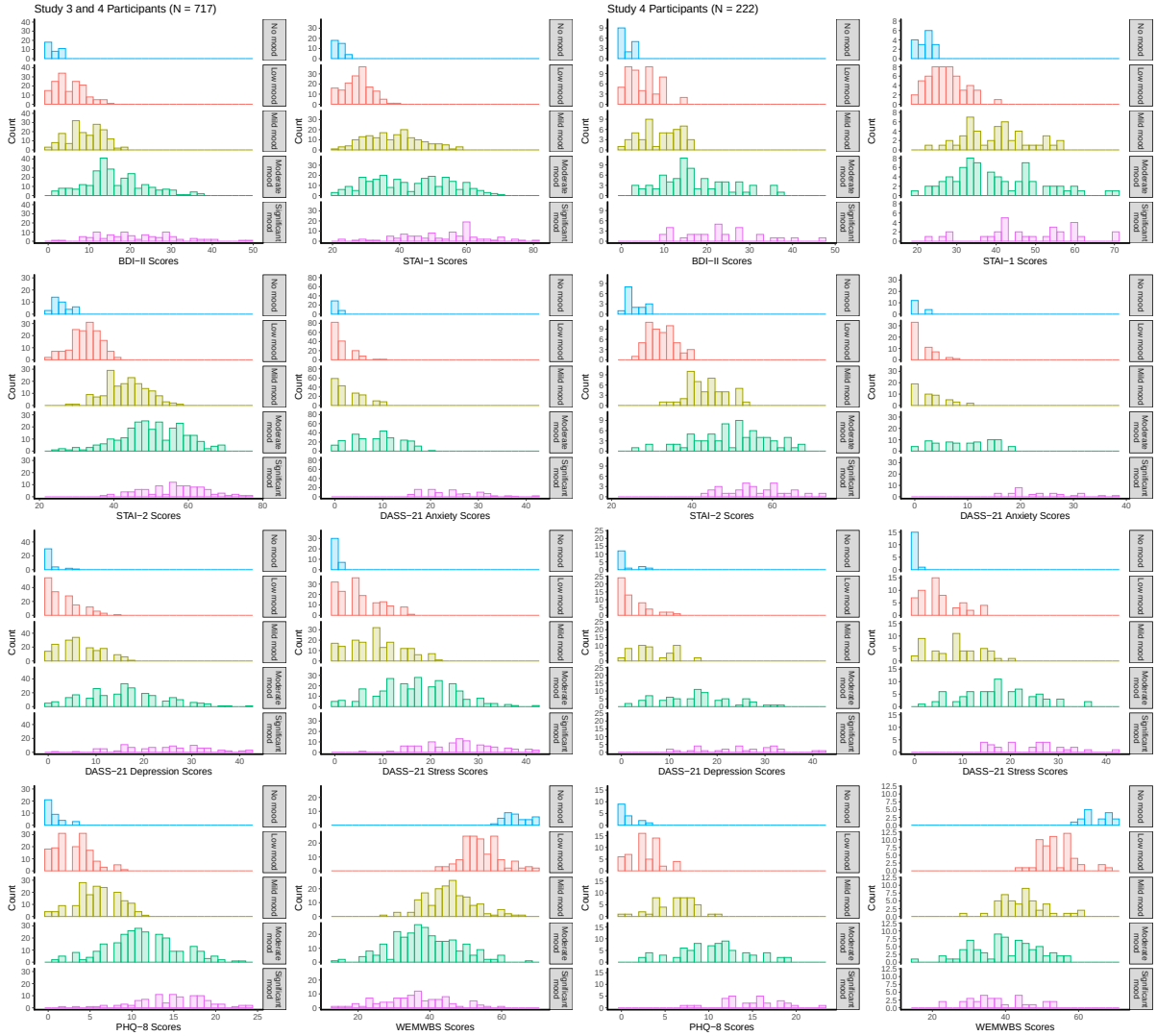
Figure A.1: Cramer's V for chi-squared test comparisons for questionnaires (df = 1). Error bars show the 95% confidence interval. The effect sizes are written in the bottom of each bar. Study 1 to Study 3 comparisons all show a medium effect size (Cramer's V > .300). Study 2 to Study 3 comparison for WEMWBS show a small effect size (Cramer's V = .258). Other comparisons show small effect sizes (.113 ≤ Cramer's V ≤ .160), except for the comparison between HSE 2016 and 2019, where no significant difference was found (Cramer's V = .047).

LPA cluster profiles

The distribution of questionnaire scores for each mental health latent profile is shown in Figure A.2 for Study 3 and 4 participants. While there are overlaps in questionnaire scores

between latent profiles, symptom severity, as indicated by higher scores, increases from "no", "low", "mild", "moderate", to "significant mood symptoms" profiles. For WEMWBS scores where higher scores indicate better mental health status, the reverse trend is observed.

Figure A.2: Distribution of questionnaire scores per questionnaire. Histograms are colour-coded per latent profile: blue - no mood symptoms, red - low mood symptoms, yellow - mild mood symptoms, green - moderate mood symptoms, purple - significant mood symptoms. (Right panel) Study 3 and 4 participants combined (N = 717), (left panel) Study 4 participants only (N = 222). From left, distributions for (top row) BDI-II scores, STAI-1 scores, (second row) STAI-2 scores, DASS-21 anxiety scores; (third row) DASS-21 depression scores, DASS-21 stress scores; (bottom row) PHQ-8 scores, WEMWBS scores. Higher scores indicate symptom severity, except for WEMWBS, where higher scores mean better mental health status.



Study 4 latent profiles Table A.2 shows a descriptive statistics of questionnaire scores per latent profile for Study 4 participants, and Table A.3 shows descriptive statistics of behavioural task performance per latent profile for Study 4 participants.

Table A.2: Descriptive statistics of questionnaire scores for Study 4 latent profiles ($N = 222$). The last three columns represent Dunn's multiple comparison Z-test statistics. Effect sizes shown as η^2 were large in all Kruskal-Wallis tests. * $p < .05$, ** $p < .01$, *** $p < .001$.

Profile	Median	Min	Max	No mood symptoms	Low mood symptoms	Mild mood symptoms	Moderate mood symptoms
BDI-II				$\chi^2(4) = 132.47$***, $\eta^2 = .592$			
No mood symptoms	0	0	4	-			
Low mood symptoms	5	0	14	2.01	-		
Mild mood symptoms	10	0	17	4.10***	3.08*	-	
Moderate mood symptoms	16	3	37	7.39***	8.19***	4.60***	-
Significant mood symptoms	22.5	9	47	7.85***	8.16***	5.36***	1.82
STAI-1				$\chi^2(4) = 108.63$***, $\eta^2 = .482$			
No mood symptoms	22.5	20	25	-			
Low mood symptoms	27	20	40	2.00	-		
Mild mood symptoms	41	22	57	6.35***	6.37***	-	
Moderate mood symptoms	38	20	71	6.30***	6.52***	0.521	-
Significant mood symptoms	47	22	70	7.34***	7.47***	1.88	2.47
STAI-2				$\chi^2(4) = 153.7$***, $\eta^2 = .690$			
No mood symptoms	25	23	29	-			
Low mood symptoms	32	26	40	2.01	-		
Mild mood symptoms	43	33	53	5.60***	5.26***	-	
Moderate mood symptoms	51	26	67	7.87***	8.92***	2.98*	-
Significant mood symptoms	56	43	73	8.51***	9.05***	4.37***	2.15
DASS-21 Anxiety				$\chi^2(4) = 147.51$***, $\eta^2 = .661$			
No mood symptoms	0	0	2	-			
Low mood symptoms	0	0	8	0.760	-		
Mild mood symptoms	2	0	10	1.92	1.71	-	
Moderate mood symptoms	10	0	18	5.49***	7.25***	5.17***	-
Significant mood symptoms	22	16	38	8.15***	10.12***	8.45***	4.66***
DASS-21 Depression				$\chi^2(4) = 149.94$***, $\eta^2 = .673$			
No mood symptoms	0	0	6	-			
Low mood symptoms	2	0	12	0.943	-		
Mild mood symptoms	6	0	16	3.41**	3.61**	-	
Moderate mood symptoms	16	2	34	6.71***	8.84***	4.67***	-
Significant mood symptoms	24	10	42	7.90***	9.56***	6.28***	2.75
DASS-21 Stress				$\chi^2(4) = 140.92$***, $\eta^2 = .631$			
No mood symptoms	0	0	2	-			
Low mood symptoms	4	0	14	2.75	-		
Mild mood symptoms	8	0	20	4.10***	2.02	-	
Moderate mood symptoms	18	2	36	7.81***	7.66***	5.23***	-
Significant mood symptoms	25	14	42	8.62***	8.28***	6.38***	2.38
PHQ-8				$\chi^2(4) = 157.97$***, $\eta^2 = .710$			
No mood symptoms	0	0	3	-			
Low mood symptoms	2	0	6	1.72	-		
Mild mood symptoms	6	0	11	4.46***	4.02***	-	
Moderate mood symptoms	10.5	2	19	7.46***	8.76***	4.15***	-
Significant mood symptoms	15	7	23	8.68***	9.66***	6.02***	2.92*
WEMWBS				$\chi^2(4) = 120.68$***, $\eta^2 = .538$			
No mood symptoms	64.5	58	70	-			
Low mood symptoms	53	43	69	-2.49	-		
Mild mood symptoms	45	28	61	-5.90***	-5.01***	-	
Moderate mood symptoms	39.5	15	57	-7.71***	-7.91***	-2.28	-
Significant mood symptoms	36	22	54	-7.55***	-7.14***	-2.72	-0.976

Table A.3: Descriptive statistics of behavioural task performance for Study 4 latent profiles. Only variables that were significant in trend analysis are shown. The last three columns represent Dunn's multiple comparison Z-test statistics. * $p < .05$, ** $p < .01$, *** $p < .001$.

Profile	N	Median	No mood symptoms	Low mood symptoms	Mild mood symptoms	Moderate mood symptoms
Stroop congruent RT variability (ms)			$\chi^2(4) = 2.23$, $\eta^2 = -.008$			
No mood symptoms	16	184	-			
Low mood symptoms	54	188	0.244	-		
Mild mood symptoms	48	181	0.300	0.0876	-	
Moderate mood symptoms	74	193	0.649	0.612	0.497	-
Significant mood symptoms	28	221	1.16	1.26	1.16	0.832
Stroop incongruent RT variability (ms)			$\chi^2(4) = 3.62$, $\eta^2 = -.002$			
No mood symptoms	16	197	-			
Low mood symptoms	54	199	0.658	-		
Mild mood symptoms	48	230	0.823	0.253	-	
Moderate mood symptoms	74	221	1.31	0.974	0.670	-
Significant mood symptoms	28	240	1.59	1.33	1.09	0.610
N-back RT (ms)			$\chi^2(4) = 5.75$, $\eta^2 = .009$			
No mood symptoms	15	743	-			
Low mood symptoms	49	682	-1.61	-		
Mild mood symptoms	42	661	-2.34	-1.09	-	
Moderate mood symptoms	61	685	-1.66	-0.0296	1.11	-
Significant mood symptoms	26	710	-1.20	0.346	1.25	0.383
Matrix Reasoning (T-score)			$\chi^2(4) = 6.92$, $\eta^2 = .014$			
No mood symptoms	16	51	-			
Low mood symptoms	54	52	1.56	-		
Mild mood symptoms	48	52	2.32	1.13	-	
Moderate mood symptoms	74	53	1.66	0.0738	-1.14	-
Significant mood symptoms	30	51.5	0.748	-0.932	-1.88	-1.04

Trend analysis

Table A.4 shows statistical results for trend analysis for Stroop, n-back, and MR.

Table A.4: Statistical summary of trend analysis, showing linear, quadratic, cubic, and quartic trends with corresponding estimates, standard error (SE), and p-values. The only significant trend for Stroop task was rt (reaction time) variability for congruent (linear and cubic trends) and incongruent trials (linear trend). For n-back, it was a quadratic trend for median reaction time, and for MR, it was a quadratic trend for T-scores. * $p < .05$, ** $p < .01$, *** $p < .001$.

			Linear			Quadratic			Cubic			Quartic		
			Estimate	SE	*p*-value	Estimate	SE	*p*-value	Estimate	SE	*p*-value	Estimate	SE	*p*-value
Stroop														
	Accuracy	Congruent	-1.10	0.989	.269	-0.260	0.914	.776	-3.92×10^{-2}	0.722	.957	-0.740	0.669	.270
		Incongruent	-0.638	0.757	.401	0.163	0.70	.816	-0.101	0.553	.855	-0.492	0.512	.338
		Difference	0.459	0.708	.518	0.423	0.655	.519	-6.22×10^{-2}	0.517	.904	0.248	0.479	.605
	Median rt	Congruent	9.18	27.90	.742	32.160	25.79	.214	1.74	20.36	.932	5.72	18.87	.762
		Incongruent	-6.18	27.57	.823	16.57	25.48	.516	-9.11	20.12	.651	0.847	18.65	.964
		Difference	-15.36	12.95	.237	-15.59	11.97	.194	-10.85	9.45	.252	-4.87	8.76	.579
	rt variability	Congruent	88.77	35.478	.013*	53.96	32.79	.101	51.194	25.89	.049*	-8.06	24.00	.737
		Incongruent	114.52	53.46	.033*	31.47	49.42	.525	21.58	39.02	.581	-28.88	36.16	.425
		Difference	25.75	37.20	.490	-22.49	34.38	.514	-29.61	27.15	.277	-20.82	25.16	.409
N-back	Accuracy		2.38	1.88	.207	-0.693	1.75	.692	0.232	1.40	.868	-0.916	1.31	.485
	Median rt		-27.21	27.82	.329	57.87	25.84	.026*	-16.74	20.66	.419	-13.68	19.36	.481
	rt variability		-9.41	14.35	.513	17.86	13.33	.182	-8.58	10.66	.422	12.20	9.99	.224
MR	T-score		1.03	1.72	.548	-4.27	1.59	.008**	6.48×10^{-2}	1.26	.959	0.966	1.18	.412

A.2 Chapter 3 Supplementary Materials

A.2.1 Methods

Participants

Exclusion criteria The second exclusion criterion for analyses was to remove participants whose mean pain ratings between TENS-off and TENS-on trials in the conditioning phase was less than 10 on the VAS. This was established due to the following reason. As 100% stimulation level is supposed to reflect a pain level of 60 on the VAS, theoretically, 60% stimulation level would be rated as 36. If participants were perfect at perceiving pain levels accurately, then the difference between trial types in the conditioning phase should be 24. However, as it is unlikely that participants perceived pain levels perfectly, a lower threshold was chosen to account for various individual differences.

Participant exclusion process Participant exclusion processes for each group are shown in Table A.5.

Table A.5: Application of the exclusion criteria. The exclusion criteria are as follows: i) failed the pain calibration, ii) was aware of the placebo-nature of the study, iii) was not successfully conditioned, iv) had missing data (questionnaire or physiological data), and v) were statistical outliers for variables of interest (initial placebo effect:rating, extinction function, initial placebo effect:aGSR). placebo:rating: initial placebo effect:rating, extinct function: extinction function, placebo:aGSR: initial placebo effect:aGSR.

Group	Initial sample	Exclusion criteria							
		i	ii	iii	iv		v		
					Questionnaire	Physiological	placebo:rating	Extinct function	placebo:aGSR
aut+alex	16	3	0	1	0	0	0	1	0
aut-alex	18	1	0	1	0	1	0	1	3
alex	16	0	0	3	0	2	0	1	1
neuro	61	4	0	2	3	2	0	3	6
Overall	111	8	0	7	3	5	0	6	10

Co-occurring diagnoses and medications Some of the autistic and alexithymic participants indicated co-occurring psychiatric conditions and medications. Out of 41 non-neurotypical participants, 21 participants (51.22%) disclosed co-occurring diagnoses. Of 21 participants, 13 participants (61.90%) were taking a median of one prescription medication. Table A.6 shows the number of diagnoses and the medications taken by participants.

Table A.6: List of diagnoses and psychotropic medications taken by non-neurotypical participants. Some of the participants had multiple diagnoses and took more than one psychotropic medications. Formal diagnoses indicate diagnoses officially determined by licensed professionals, whereas informal diagnoses include non-formal diagnoses by licensed professionals and self-diagnoses. SSRI: Selective serotonin reuptake inhibitor, SNRI: Serotonin-noradrenaline reuptake inhibitor.

Psychiatric Diagnoses

Name	Total *N*	Diagnosis type		Medications taken	
		Formal	Informal	Yes	No
ADHD	2	2	0	2	0
Anxiety	9	8	1	6	3
Bipolar Disorder	1	1	0	0	1
Bulimia	1	1	0	0	1
Depression	7	7	0	6	1
Dissociative identity disorder	1	1	0	0	1
OCD	2	1	1	1	1
Schizophrenia	1	1	0	1	0

Psychotropic Medications

Purpose	Total *N*	*n*	Name	Class	Affected neuromodulators
Anticonvulsant	2	2	Pregabalin	Anxiolytic	Presynaptic modulatory effect over excitatory neurons
Anti-anxiety	1	1	Propranolol	Beta-blocker	Adrenaline, noradrenaline
Antidepressant	7	1	Citalopram	SSRI	Serotonin
		1	Fluoxetine	SSRI	Serotonin
		1	Mirtazapinee	Tetracyclic	Noradrenaline, serotonin
		2	Setraline	SSRI	Serotonin
		2	Venlafaxine	SNRI	Noradrenaline, serotonin
Antipsychotic	1	1	Quetiapine	Atypical	Dopamine, serotonin
Stimulant	3	1	Lisdexamfetamine	Stimulant	Noradrenaline
		2	Methylphenidate	Stimulant	Dopamine, noradrenaline

Verbal instructions

All participants were provided with an information sheet about the purpose and the function of the TENS when they contacted the researcher about participating in the study. Prior to starting the behavioural task, participants received the following verbal instructions.

"This is the TENS electrode [researcher shows the participant the placebo device]. TENS stands for transcutaneous electrical nerve stimulation. TENS can reduce pain by inhibiting the pain signals that travel up your arm and into your brain. The TENS itself is not painful, but you will feel a small sensation when it's turned on.

During this experiment, you will receive electrical shock stimulations similar to those you received during the calibration. Sometimes the TENS device will be turned on before the shock (as indicated by a green cross) and should reduce your pain. After each shock, you will be asked to rate the intensity of your pain using a scale. You will then wait a bit before the next shock. Please do not talk to the experimenter during the task unless you feel uncomfortable and would like to stop.

Before each trial you will wait a few seconds. Then you will see a black cross indicating the start of a trial. This cross will either turn red (TENS-off) or green (TENS-on). You will be asked to name the colour of the cross and after a few seconds you will receive the shock. You will then see a blank screen for a few seconds and then you will be asked to rate the intensity of the pain you experienced during the shock."

Exit questionnaire

An exit questionnaire was used to test the participants' knowledge of the placebo-shock reduction contingency across groups, as well as whether they were aware of the true nature of the study. This was conducted verbally by the experimenter. First, participants were asked, "In the first [or second] half of the experiment, did you notice any reduction in pain when TENS was turned on compared with when it was not turned on?" They had to make a forced choice response, either "yes" or "no" and then rate the consistency on a scale from 1 (not at all consistent) to 10 (very consistent). Then they were asked, "What do you think the study was about?" with an open response, as well as an opportunity to provide any observations they had made related to electric shocks or the TENS device. Participants were also asked for any psychiatric or neurological diagnoses, as well as any medications taken on a regular basis.

A.2.2 Results

Descriptive statistics

Group comparisons on self-report measures were performed with one-way ANOVA if the residuals were normally distributed, with Tukey's post-hoc used where appropriate. Otherwise Kruskal-Wallis test was performed, with Dunn's test with Bonferroni corrections where appropriate. Only significant pair-wise comparisons are noted below.

There was a statistically significant group difference in age [$\chi^2(3) = 16.01, p = .001$]. Dunn's test revealed that the nt group was significantly younger than the aut-alex group [$Z = -7.59, p = .042$].

As expected, there were statistically significant group differences in AQ-50 [$F(3) = 50.66, p$

< .001]. Tukey's post-hoc test revealed that AQ-50 was lower in i) the alex than in the aut+alex group [difference = -14.19, $p < .001$], ii) the nt than in the aut+alex group [difference = -25.14, $p = .000$], iii) the nt than in the aut-alex group [difference = -17.66, $p = .000$], and iv) the nt than in the alex group [difference = -10.96, $p < .001$].

Similarly, there was a statistically group effect in TAS-20 [$F(3) = 87.80$, $p < .001$]. Tukey's post-hoc test showed that TAS-20 was lower in i) the aut-alex than in the aut+alex group [difference = -26.90, $p = .000$], ii) the aut-alex than in the alex group [difference = -21.58, $p = .000$], iii) the nt than in the aut+alex group [difference = -34.79, $p = .000$], iv) the nt than in the aut-alex group [difference = -7.90, $p = .006$], v) the nt than in the alex group [difference = -29.48, $p = .000$].

There was statistically significant group difference in STAI-1 [$\chi^2(3) = 17.40$, $p < .001$]. Pair-wise comparisons showed that the nt group had lower state anxiety than the aut+alex group [$Z = -3.45$, $p = .003$], and the aut-alex group [$Z = -2.98$, $p = .018$].

There was statistically significant group difference in STAI-2 [$\chi^2(3) = 35.77$, $p < .001$]. Pair-wise comparisons showed that the nt group had lower trait anxiety than the aut+alex group [$Z = -3.45$, $p = .003$], and the aut-alex group [$Z = -2.98$, $p = .018$].

There was statistically significant group difference in BDI-II [$\chi^2(3) = 22.14$, $p < .001$]. Pair-wise comparisons showed that the nt group had lower depressive traits than the rest of the groups: i) the aut+alex group [$Z = -3.27$, $p = .006$], ii) the aut-alex group [$Z = -3.20$, $p = .008$], and iii) the alex group [$Z = -3.15$, $p = .010$].

There was a statistically significant group difference in BPQs-A [$F(3) = 3.25$, $p = .025$], and the only significant pair-wise comparison was where the nt group had lower bodily awareness than the aut-alex group [difference = -7.59, $p = .042$].

There was a statistically significant group difference in PCS [$\chi^2(3) = 6.40$, $p = .094$], but none of the pair-wise comparisons were significant. There was a statistically significant difference between groups in FSIQ [$F(3) = 3.20$, $p = .030$], but none of the pair-wise comparisons survived. There was no significant group difference in stimulation level [$\chi^2(3) = 1.54$, $p = .672$].

Extinction function

Extinction function plotted for each participant can be found in Fig A.3. While the majority of participants have simple functions (77.08% participants overall have edf < 1), for some participants, the extinction process is not straight-forward, with the most complicated function having an edf of 7.15.

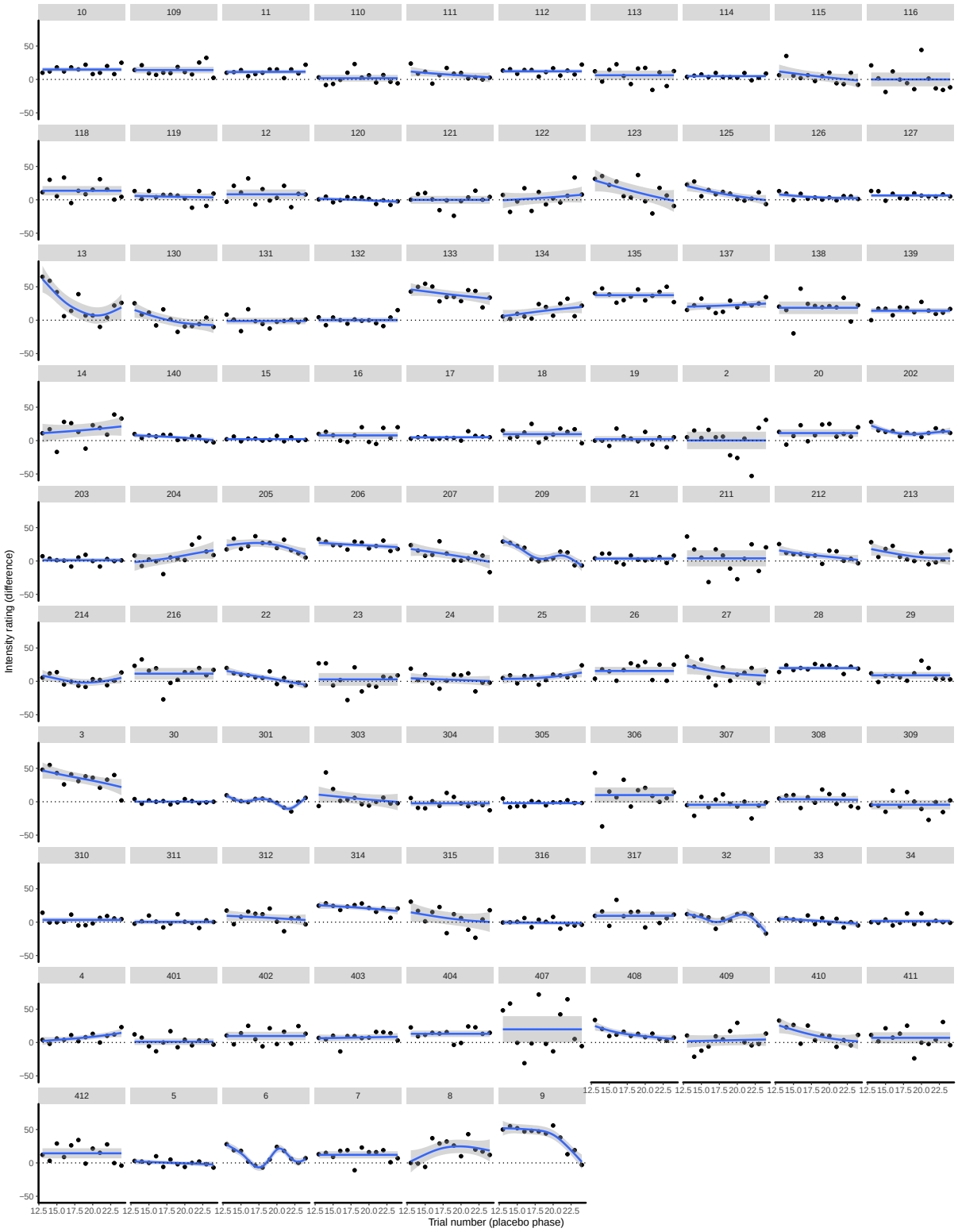


Figure A.3: A scatterplot showing the extinction function per participant. The shaded region represents the 95% confidence interval, and each dot represents a trial. The dotted vertical line indicates the absence of a placebo effect. Any points above the dotted line suggests the presence of the placebo effect, and those below the line is indicative of the nocebo effect.

A.3 Chapter 4 Supplementary Materials

A.3.1 Methods

Prediction error task trial composition

The trial composition for the prediction error task is shown in Table A.7. The task consisted of 5 blocks of 24 trials, with a self-timed break in-between blocks. Each block consisted of one of all trial types for cues 2 and 8, and two trials for cues 3 through 7.

Table A.7: Trial composition for the prediction error size task. Cue type indicates whether the trial was veridical or non-veridical. Veridical cue type means that the prediction error was 0, meaning that the cue indicated the true intensity level of the upcoming stimulation. Non-veridical cue type means that the prediction error was not 0, ranging from -6 to +6.

Cue	Cue type	Stimulus intensity	Prediction error	Number of trials	
				Block	Total
2	Veridical	2	0	1	5
	Non-veridical	3	1	1	5
		4	2	1	5
		5	3	1	5
		6	4	1	5
		7	5	1	5
		8	6	1	5
3	Veridical	3	0	2	10
4		4	0	2	10
5		5	0	2	10
6		6	0	2	10
7		7	0	2	10
8	Veridical	8	0	1	5
	Non-veridical	7	-1	1	5
		6	-2	1	5
		5	-3	1	5
		4	-4	1	5
		3	-5	1	5
		-6	-6	1	5

A.3.2 Results

Descriptive statistics

Group comparisons on self-report measures were performed with a two-way ANOVA, with Tukey's post-hoc used where appropriate. Only significant pair-wise comparisons are noted below.

There was a statistically significant difference in age by autism group [$F(1) = 11.25$, $p = .001$], where the non-autism group was younger than the autism group [difference = -7.37, $p < .001$]. There was no difference by alexithymia group [$F(1) = 6.46 \times 10^{-2}$, $p = .800$].

As expected, there was a statistically significant difference in AQ-50 by autism group [$F(1) = 55.59$, $p < .001$], where the non-autism group had lower autistic traits than the autism group [difference = -14.44, $p = .000$]. There was also a significant difference by alexithymia group [$F(1) = 18.81$, $p < .001$], where the non-alexithymia group had lower autistic traits than the alexithymia group [difference = -6.97, $p < .001$].

There was no statistically significant difference in TAS-20 by autism group [$F(1) = 2.00$, $p = .162$]. As expected, there was a significant difference by alexithymia group [$F(1) = 136.36$, $p < .001$], where the non-alexithymia group had lower alexithymic traits than the alexithymia group [difference = -21.70, $p = .000$].

There was no statistically significant difference in STAI-1 by autism group [$F(1) = 2.88$, $p = .094$]. There was a significant difference by alexithymia group [$F(1) = 5.12$, $p = .027$], where the non-alexithymia group had lower state anxiety than the alexithymia group [difference = -5.28, $p = .032$].

There was also no statistically significant difference in STAI-2 by autism group [$F(1) = 2.29$, $p = .135$]. There was, however, a significant difference by alexithymia group [$F(1) = 22.93$, $p < .001$], where the non-alexithymia group had lower trait anxiety than the alexithymia group [difference = -10.81, $p < .001$].

There was a statistically significant difference in BDI-II by autism group [$F(1) = 4.85$, $p = .031$], where the non-autism group had lower depressive traits than the autism group [difference = -5.74, $p = .002$]. There was also a significant difference by alexithymia group [$F(1) = 14.28$,

$p < .001$], where the non-alexithymia group had lower depressive traits than the alexithymia group [difference = -6.57, $p < .001$].

There was a statistically significant difference in PCS by autism group [$F(1) = 6.96$, $p = .010$], where the non-autism group had lower pain catastrophising trait than the autism group [difference = -8.80, $p < .001$]. There was also a significant difference by alexithymia group [$F(1) = 11.79$, $p < .001$], where the non-alexithymia group catastrophised pain less than the alexithymia group [difference = -8.23, $p = .001$].

There was a statistically significant difference in IAS by autism group [$F(1) = 7.05$, $p = .010$], where the non-autism group had higher interoceptive accuracy than the autism group [difference = 9.93, $p = .002$]. There was no significant difference by alexithymia group [$F(1) = 3.93$, $p = .051$].

There was no statistically significant difference in IUS-12 by autism group [$F(1) = 1.46$, $p = .231$]. There was a significant difference by alexithymia group [$F(1) = 16.94$, $p < .001$], where the non-alexithymia group had less intolerance of uncertainty than the alexithymia group [difference = -7.44, $p < .001$].

There were no statistically significant differences in BPQs-A by autism group [$F(1) = 0.185$, $p = .668$], nor by alexithymia group [$F(1) = 4.00 \times 10^{-4}$, $p = .983$]. The same was the case for IATS, where no significant differences by autism group [$F(1) = 8.15 \times 10^{-2}$, $p = .776$], nor by alexithymia group [$F(1) = 1.11$, $p = .300$] were found. Similarly, there were no significant differences in FSIQ by autism group [$F(1) = 2.69 \times 10^{-2}$, $p = .870$], nor by alexithymia group [$F(1) = 4.62 \times 10^{-2}$, $p = .831$].

Relationship between prediction error and subjective error

Subjective error plotted against prediction error for each participant can be found in Fig A.4. While some participants have a quartic relationship (e.g. Participant 4, 43), some have a linear relationship (e.g. Participant 46, 206).

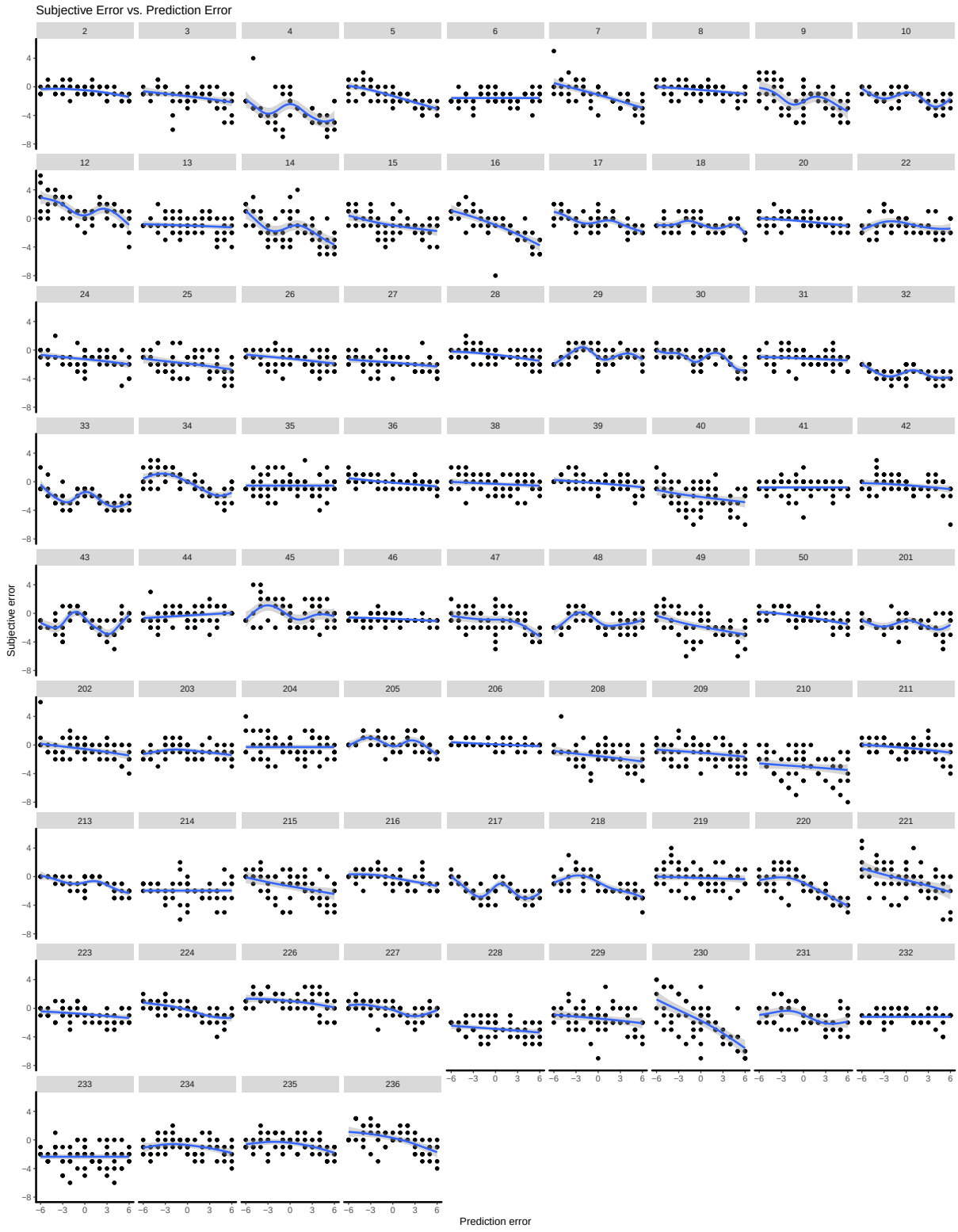


Figure A.4: Relationship between prediction error and subjective error per participant. The shaded region represents the 95% confidence interval, and each dot represents a trial. Individual differences in the relationship between prediction error and subjective error are observed: some participants showed somewhat a linear relationship (e.g., Participant 24, 25), whereas some demonstrated a quartic relationship indicative of the "tipping point" phenomenon (e.g., Participant 34, 231).

A.4 Chapter 5 Supplementary Materials

A.4.1 Methods

Exclusion criteria

The participant sample for Studies 1 and 2.1-2.5 are shown in Table A.8, before and after the application of exclusion criteria as listed in Section 5.2.1.

Table A.8: Application of the exclusion criteria. The exclusion criteria are as follows: i) did not meet the inclusion criteria, ii) had incomplete questionnaire data, iii) failed calibration, iv) failed cue check, v) scored below 80% in the practice task, vi) scored below 80% in the attention check trials within the main task, vii) incorrectly responded to the attention check questionnaire, and viii) had more than 10% of the trials removed. Exclusion criteria v) through vii) are only applicable for Study 2. Exclusion criterion viii) is only applicable for Studies 1 and 2.5. Final sample size for autism and alexithymia groups in Study 2.5 are included, but these groups were not treated separately due to the small sample size.

Study	Group	Initial sample	Exclusion criteria								Final sample
			i	ii	iii	iv	v	vi	vii	viii	
1.0	aut+alex	18	0	0	1	0	-	-	-	2	15
	aut-alex	15	0	0	1	0	-	-	-	2	12
	alex	14	0	0	0	0	-	-	-	1	13
	nt	40	0	3	1	0	-	-	-	0	36
2.1	nt	60	3	0	0	2	14	0	3	-	38
2.2		47	4	0	0	0	7	0	0	-	38
2.3		7	0	0	1	0	2	0	0	-	4
2.4		8	0	0	1	0	1	0	0	-	3
2.5	nt	225	0	1	16	2	75	1	0	10	120
	autism	16	0	0	0	0	3	1	0	0	12
	alexithymia	20	0	0	1	0	2	0	0	1	16

Overall task-based exclusion criteria Stringent participant exclusion criteria were applied for Studies 2.1-2.5, which were conducted online and during the COVID-19 pandemic. Previous studies have suggested issues with data quality in online research (Douglas et al., 2023; Peer et al., 2021; Webb & Tangney, 2022). During the COVID-19 pandemic, however, there were especially wide discrepancies in the online research data quality. For this reason, in addition to attention checks, participants were only included in the analysis if they scored above 80% in the practice task. This threshold was decided based on Wiech et al.'s (2014) results, where participants scored above 80% on average in all conditions in the paradigm that was used in the

present study.

Trial-based exclusion criteria Any trials that met the exclusion criteria as outlined in Section 5.2.3 were removed prior to analysis. Exclusion criteria were as follows: i) the experimenter failed to change the stimulation level to the appropriate one, ii) the participant did not make a response, and iii) any trial where the absolute z-score transformed reaction time was greater than 3. If participants had more than 10% of the trials removed, that participant was removed from all analyses. For Study 1, 5 participants were removed as they had between 12.50% and 31.25% of trials removed (2 aut+alex, 2 aut-alex, 1 alex). For Study 2.5, 11 participants were removed as they had between 10.67% and 24.33% of trials removed. The summary of trial removal for participants who remained in the analysis can be found in Table A.9.

Table A.9: Application of trial-based exclusion criteria for Studies 1 and 2.5. Bad trial is where the experimenter failed to change the stimulation level to the appropriate one, or the participant did not make a response. Bad reaction time is where the absolute z-score transformed reaction time was greater than 3. Proportions of trials that were removed overall are also noted.

	Study 1					**Study 2.5**
	aut+alex *n* = 15	aut-alex *n* = 12	alex *n* = 13	nt *n* = 36	Overall *N* = 76	 *N* = 148
Bad trial						
Mean (SD)	1.08 (1.04)	1.20 (1.78)	0.433 (0.968)	0.851 (1.30)	0.880 (1.29)	1.26 (1.50)
Median [Min, Max]	0.625 [0, 2.50]	0.313 [0, 5.63]	0 [0, 3.13]	0.625 [0, 6.88]	0.625 [0, 6.88]	0.667 [0, 8.67]
Bad reaction time						
Mean (SD)	0.714 (1.49)	0.698 (1.19)	0.288 (0.548)	0.402 (1.21)	0.491 (1.17)	1.07 (1.16)
Median [Min, Max]	0 [0, 5.63]	0 [0, 3.23]	0 [0, 1.88]	0 [0, 6.88]	0 [0, 6.88]	0.676 [0, 6.55]
Overall removed trials						
Mean (SD)	1.79 (1.72)	1.88 (2.65)	0.721 (0.983)	1.25 (1.76)	1.37 (1.82)	2.32 (2.17)
Median [Min, Max]	1.25 [0, 5.63]	0.625 [0, 8.13]	0.625 [0, 3.13]	0.625 [0, 7.50]	0.625 [0, 8.13]	1.67 [0, 9.67]

A.4.2 Results

Descriptive statistics

Study 1 (pain) Kruskal-Wallis test was used to assess group differences for non-normally distributed variables, followed by Dunn's test where appropriate. For normally distributed variables, one-way ANOVA and Tukey's test were used. Only significant pair-wise comparisons are noted below.

There was a statistically significant difference in age by group [$\chi^2(3) = 19.62$, $p < .001$]. The aut+alex group was significantly older than i) the alex group [$Z = 3.07$, $p = .013$] and ii) the nt group [$Z = 4.16$, $p < .001$].

There was a statistically significant group difference in AQ-50 [$\chi^2(3) = 31.16$, $p < .001$]. The aut+alex group had higher autistic traits than i) the alex group [$Z = 2.85$, $p = .026$], and ii) the nt group [$Z = 5.41$, $p < .001$]. The aut-alex group also had greater autistic traits than the nt group [$Z = 2.79$, $p = .032$].

There was a statistically significant group difference in TAS-20 [$\chi^2(3) = 54.13$, $p < .001$]. The aut+alex group had higher alexithymic traits than i) the aut-alex group [$Z = 3.46$, $p = .003$], and ii) the nt group [$Z = 5.71$, $p < .001$]. The alex group also had higher alexithymic traits than i) the aut-alex group [$Z = 3.73$, $p = .001$], and ii) the nt group [$Z = 5.89$, $p < .001$].

There was a statistically significant group difference in STAI-1 [$\chi^2(3) = 11.86$, $p = .008$], where the aut+alex group had higher state anxiety than the nt group [$Z = 3.25$, $p = .007$].

There was a statistically significant group difference in STAI-2 [$\chi^2(3) = 26.68$, $p < .001$], where the nt group had less trait anxiety than i) the aut+alex group [$Z = -4.17$, $p < .001$], and ii) the alex group [$Z = 4.08$, $p < .001$].

There was a statistically significant group difference in BDI-II [$\chi^2(3) = 11.73$, $p = .008$], where the nt group was less depressed than i) the aut+alex group [$Z = -2.70$, $p = .042$], and ii) the alex group [$Z = -2.78$, $p = .033$].

There was a statistically significant group difference in PCS [$F(3) = 3.71$, $p = .002$], where the nt group had lower pain catastrophising trait than the aut+alex group [difference = -10.36, $p = .011$].

There was a statistically significant difference in IAS by group [$F(3) = 6.27$, $p < .001$], where the nt group had greater self-reported interoceptive accuracy than the aut+alex group [difference = 16.06, $p < .001$].

There was a statistically significant difference in IUS-12 by group [$F(3) = 8.97$, $p < .001$], where the nt group had less intolerance of uncertainty than i) the aut+alex group [difference = -10.68, $p < .001$], and ii) the alex group [difference = -9.37, $p = .002$].

There were no statistically significant group differences in BPQs-A [$F(3) = 0.677$, $p = .569$],

IATS [$F(3) = 0.220$, $p = .882$], and FSIQ [$\chi^2(3) = 5.24$, $p = .155$].

Study 2.1 to 2.4 (vision) Table A.10 summarises the participant demographic information for Studies 2.1 through 2.4, which were the paradigm development studies.

Table A.10: Descriptive statistics for Studies 2.1-2.4. IUS-12 and MR were optional, and therefore there are some participants who did not complete them. The proportions of missing data for IUS-12 and MR (T-score) are shown as result.

	Study 2.1 *N* = 38	Study 2.2 *N* = 38	Study 2.3 *N* = 4	Study 2.4 *N* = 3
Age				
Mean (SD)	24.9 (9.15)	32.1 (10.2)	33.0 (10.7)	28.3 (9.29)
Median [Min, Max]	20.0 [18.0, 50.0]	33.0 [18.0, 50.0]	28.5 [26.0, 49.0]	24.0 [22.0, 39.0]
Gender				
Female	21 (55.3%)	26 (68.4%)	3 (75.0%)	2 (66.7%)
Male	17 (44.7%)	12 (31.6%)	1 (25.0%)	1 (33.3%)
AQ-50				
Mean (SD)	29.0 (11.5)	32.1 (9.72)	16.5 (12.9)	11.0 (8.19)
Median [Min, Max]	33.0 [2.00, 46.0]	35.0 [2.00, 46.0]	15.5 [2.00, 33.0]	13.0 [2.00, 18.0]
TAS-20				
Mean (SD)	43.1 (10.3)	43.6 (13.1)	49.5 (5.45)	40.7 (11.7)
Median [Min, Max]	43.5 [25.0, 70.0]	41.0 [24.0, 75.0]	48.5 [44.0, 57.0]	36.0 [32.0, 54.0]
STAI-1				
Mean (SD)	39.2 (12.7)	33.3 (12.5)	31.5 (5.92)	34.0 (8.66)
Median [Min, Max]	36.5 [20.0, 64.0]	31.0 [20.0, 70.0]	29.5 [27.0, 40.0]	39.0 [24.0, 39.0]
STAI-2				
Mean (SD)	43.9 (10.8)	37.6 (11.6)	48.5 (11.7)	53.0 (13.9)
Median [Min, Max]	44.0 [22.0, 62.0]	35.5 [23.0, 65.0]	54.0 [31.0, 55.0]	60.0 [37.0, 62.0]
BDI-2				
Mean (SD)	10.3 (8.07)	7.39 (7.98)	16.8 (3.95)	15.7 (17.2)
Median [Min, Max]	10.0 [0, 31.0]	5.50 [0, 29.0]	18.0 [11.0, 20.0]	13.0 [0, 34.0]
PCS				
Mean (SD)	21.0 (13.0)	19.9 (11.5)	33.0 (13.1)	27.0 (14.2)
Median [Min, Max]	21.0 [0, 51.0]	18.0 [0, 41.0]	31.5 [19.0, 50.0]	32.0 [11.0, 38.0]
IAS				
Mean (SD)	85.3 (11.5)	87.5 (12.7)	87.5 (8.19)	88.3 (12.2)
Median [Min, Max]	90.0 [60.0, 103]	90.0 [52.0, 105]	89.5 [76.0, 95.0]	91.0 [75.0, 99.0]
IATS				
Mean (SD)	44.2 (15.9)	43.5 (19.7)	59.8 (29.1)	42.7 (17.6)
Median [Min, Max]	43.0 [21.0, 82.0]	37.0 [21.0, 98.0]	56.5 [30.0, 96.0]	45.0 [24.0, 59.0]
IUS-12				
Mean (SD)	33.6 (10.2)	34.0 (10.7)	3/1/39	40.0 (2.83)
Median [Min, Max]	32.0 [15.0, 58.0]	32.0 [16.0, 55.0]	34.0 [32.0, 52.0]	40.0 [38.0, 42.0]
Missing	15 (39.5%)	5 (13.2%)	1 (25.0%)	1 (33.3%)
MR				
Mean (SD)	54.0 (7.43)	52.5 (9.70)	54.3 (3.79)	51.0 (7.07)
Median [Min, Max]	54.0 [38.0, 73.0]	52.0 [27.0, 72.0]	56.0 [50.0, 57.0]	51.0 [46.0, 56.0]
Missing	15 (39.5%)	5 (13.2%)	1 (25.0%)	1 (33.3%)

Studies 2.1 to 2.4 task performance

Task performance (accuracy and reaction time) is illustrated in Figure A.5. Mean values for task performance variables can be found in Table A.11.

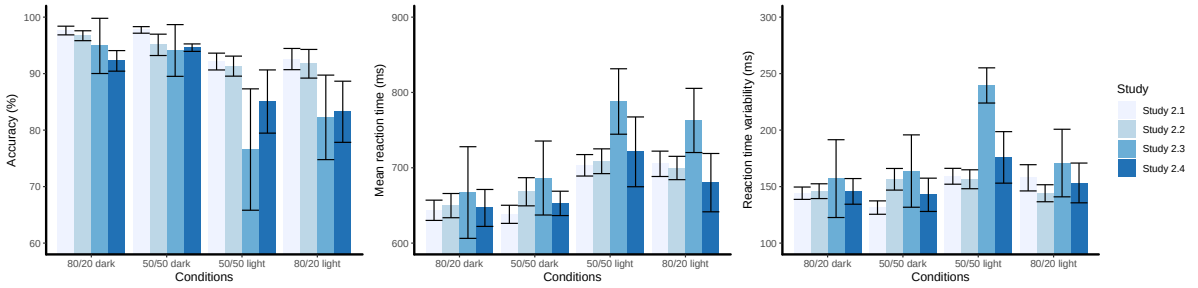


Figure A.5: Task performance for Studies 2.1-2.4. Bar plots show (left) accuracy, (middle) mean reaction time, and (right) reaction time variability. The shade of bar plots gets darker for later versions of study development, with Study 2.1 being the lightest shade of blue and Study 2.4 being the darkest shade of blue. 80/20 indicates that participants saw a cue with a probabilistic value of 80% chance of seeing a dark image and 20% chance of seeing a light image after cue presentation. 50/50 indicates that participants saw a cue with a probabilistic value of 50% chance of seeing a dark or light image after cue presentation. Dark or light indicates the intensity of the image.

Table A.11: Means of task performance variables for Studies 2.1-2.4.

			Accuracy (%)		Reaction time (ms)			
					Mean		Variability	
	Study	*N*	Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]	Mean (SD)	Median [Min, Max]
80/20 dark	2.1	38	97.6 (4.74)	98.8 [72.4, 100]	644 (82.9)	644 [503, 928]	144 (33.7)	149 [72.0, 207]
	2.2	38	96.7 (5.40)	99.1 [74.4, 100]	650 (99.1)	640 [487, 983]	146 (40.3)	142 [80.3, 239]
	2.3	4	94.9 (9.77)	99.7 [80.3, 100]	667 (122)	612 [596, 849]	157 (68.9)	129 [111, 259]
	2.4	3	92.3 (3.15)	91.8 [89.4, 95.6]	647 (42.5)	659 [600, 682]	146 (19.7)	142 [129, 167]
50/50 dark	2.1	38	97.7 (3.59)	99.0 [83.3, 100]	638 (74.1)	632 [526, 933]	131 (36.5)	122 [70.3, 227]
	2.2	38	95.1 (11.6)	100 [45.5, 100]	668 (115)	647 [488, 1150]	156 (59.0)	148 [53.9, 301]
	2.3	4	94.1 (9.16)	98.0 [80.4, 100]	686 (98.2)	644 [625, 833]	164 (64.0)	165 [88.5, 237]
	2.4	3	94.6 (1.14)	94.0 [93.9, 95.9]	653 (28.0)	637 [636, 685]	143 (25.5)	143 [117, 168]
50/50 light	2.1	38	92.1 (9.17)	94.7 [53.2, 100]	703 (87.8)	702 [562, 932]	159 (43.3)	155 [69.7, 236]
	2.2	38	91.3 (10.9)	94.0 [44.9, 100]	709 (101)	694 [529, 1060]	157 (51.6)	148 [73.4, 313]
	2.3	4	76.6 (21.5)	76.0 [56.3, 98.0]	788 (86.9)	771 [702, 908]	240 (31.1)	240 [201, 277]
	2.4	3	85.1 (9.69)	81.6 [77.6, 96.0]	721 (80.2)	697 [655, 811]	176 (39.5)	159 [148, 221]

Study 2.1 Task accuracy was higher for dark than light images in the 50/50 condition [$t(37) = 3.99$, $p < .001$, 95% CI: 2.75×10^{-2}, 8.45×10^{-2}]. However, there was no significant difference in accuracy for dark images between the 80/20 and 50/50 conditions [$t(37) = 0.242$, $p = .810$, 95% CI: -7.96×10^{-3}, 1.01×10^{-2}]. Upon checking for ceiling effect, it was found that 29 participants scored 99% or higher in at least one of the conditions (80/20 dark, 80/20 light,

50/50 dark, 50/50 light). In fact, two participants scored 100% in all conditions. It was therefore determined that the task difficulty needed to be increased.

Study 2.2 There were no significant differences in accuracy i) for dark images between the 80/20 and 50/50 conditions [$t(37)$ = -1.04, p = .304, 95% CI: -4.76×10^{-2}, 1.52×10^{-2}], and ii) between dark and light images in the 50/50 condition [$t(37)$ = 1.61, p = .116, 95% CI: -9.80×10^{-3}, 8.52×10^{-2}]. When checking for ceiling effects, 33 participants scored 99% or higher in at least one of the conditions, three of whom scored 100% in all conditions. The task difficulty was increased again as result.

Study 2.3 There were no significant differences in accuracy in any of the condition comparisons: i) for dark images between the 80/20 and 50/50 conditions [$t(3)$ = -1.50, p = .230, 95% CI: -2.52×10^{-2}, 9.02×10^{-3}], and ii) between dark and light images in the 50/50 condition [$t(3)$ = 2.07, p = .130, 95% CI: -9.40×10^{-2}, 0.445]. When checking for ceiling effects, it was found that none of the participants scored 99% or higher in all four conditions. When the ceiling effect threshold was lowered to accuracy of 95% or higher, one participant scored above 95% in all four conditions. The task difficult was increased again.

Study 2.4 There were no significant differences in accuracy for any of the condition comparisons: i) for dark images between the 80/20 and 50/50 conditions [$t(2)$ = 1.18, p = .360, 95% CI: -6.20×10^{-2}, 0.109], and ii) between dark and light images in the 50/50 condition [$t(2)$ = 1.57, p = .257, 95% CI: -0.166, 0.357]. For ceiling effects, all participants scored above 95% in just one of the conditions. The task difficulty was deemed sufficient, and Study 2.5 was conducted with the same experimental conditions, as it was assessed that the lack of significant results from t-tests were due to the small sample size (N = 3).

Task performance distributions

Figure 5.4 shows distribution of reaction time (correct and incorrect trials, separately), and accuracy for Studies 1 (pain) and 2.5 (vision).

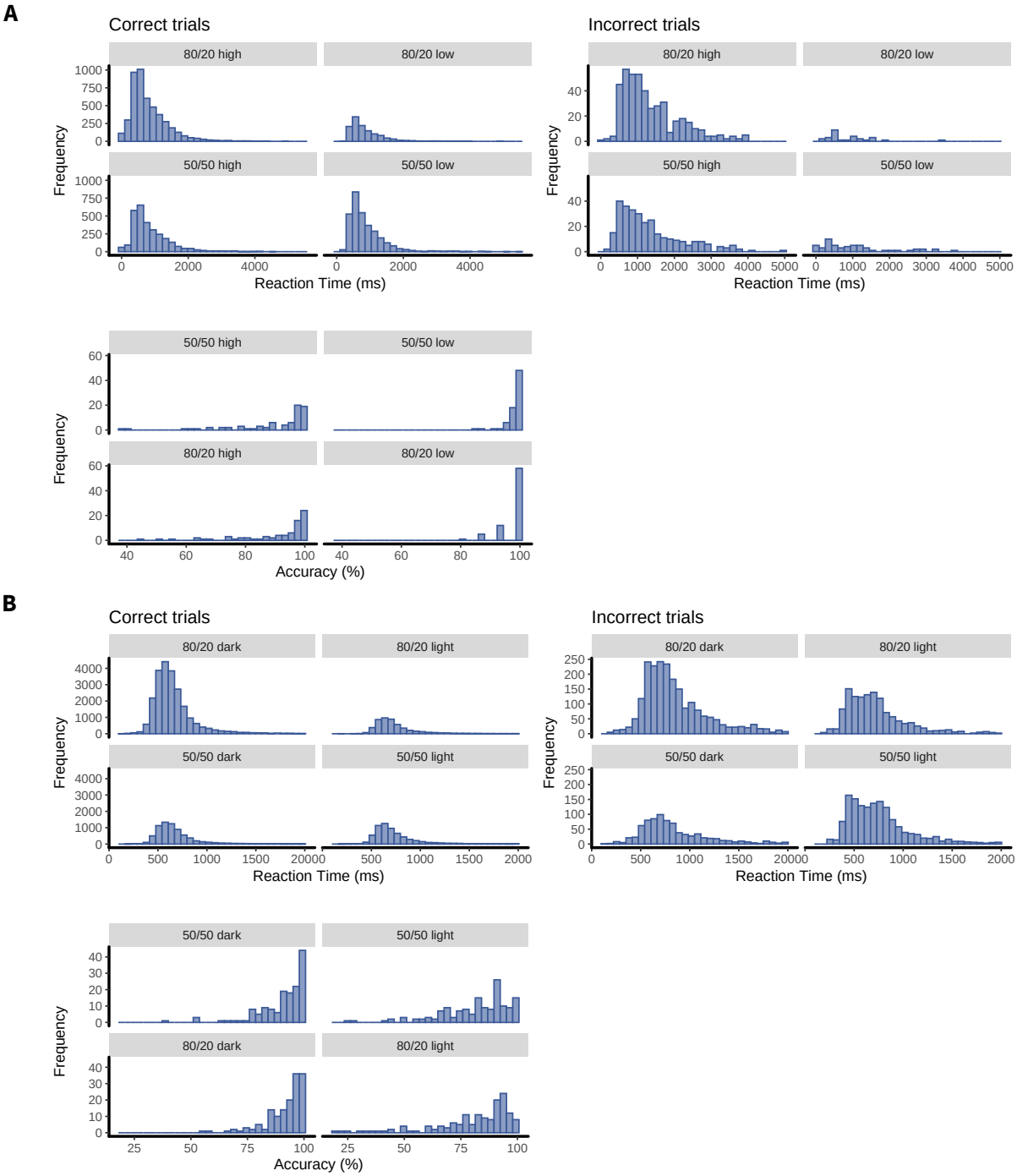


Figure A.6: Task performance distribution for (A) Study 1 (pain) and (B) Study 2.5 (vision). (Top row) Reaction time distribution for (left) correct and (right) incorrect trials. (Bottom row) Task accuracy. Each variable is shown per condition. High/low and dark/light indicate the outcome. 80/20 and 50/50 indicate the probabilistic outcome associated with the cue presented.