Pain in Autism Spectrum Disorder.

Sarah Vaughan

A thesis submitted in partial fulfilment of the requirements of Liverpool John Moores University for the Degree of Philosophy

March 2021

List of Tables

List of Figures

Acknowledgments

First and foremost, I am extremely grateful too, and would like to thank my director of studies Dr David Moore, for introducing me to the field of pain and autism. Thank you for the invaluable advice and continuous support throughout my PhD. On a very personal note, my appreciation for the honesty with which conversations occurred. This is an invaluable quality, which I only hope to emulate with others in my career. I would also like to thank Professor Francis McGlone, for his modelling of critical thinking and my invaluable time spent with the SomAffect Lab group. You will all (SomAffect team) never know just how much those days spent discussing all aspects of research mean to me. To Dr Helen Poole for her continued insights on my PhD and feedback that helped me to elevate my work, again my deepest gratitude. A particular mention to all those PhD's with whom I crossed paths, all of which made my time at LJMU memorable and who created a home from home for me. But particularly to those whose continued friendship I am forever blessed with, Dr Andrea Piovesan, Dr Deborah Talamonti and Dr Jamie Tully, to name a few. To Dr Susannah Walker and Dr Michelle Failla, my deepest gratitude to you both for being my examiners.

Outside of Liverpool John Moores University, I would like to extend my appreciation and deepest thanks to those who supported me both academically and personally. There needs to be a special mention to Robert Williams and Dr Clea Wright for acting as models for me, while I photographed them faking pain. To Dr Glenys Holt for her proof reading and ear when I needed to work through all my thoughts, yet another friend with whom I have been blessed. To, my family, especially to Bob, Paul and Mozza. Their financial and emotional support made this possible. I am forever indebted to them and would not be where I am today without their constant encouragement.

Research Publications

The research that was conducted in relation to this PhD, including Experiment 2 has led to the following publications:

- Based on Experiment 2, Chapter 2:

Vaughan, S., McGlone, F., Poole, H. et al. (2019). A Quantitative Sensory Testing Approach to Pain in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders, 50*, 1607-1920. https://doi.org/10.1007/s10803-019-03918-0 (see Appendix A)

- Based on research work conducted in preparation for the PhD:

Vaughan, S., Failla, M., Poole, H. et al. (2019). Pain Processing in Psychiatric Conditions: A Systematic Review. *Review of General Psychology, 23*(3), 336-358. https://doi.org/10.1177/1089268019842771 (see Appendix B)

Contributions

This section is to confirm that myself, Sarah Vaughan, the author of this thesis, was actively involved and made a significant contribution to all chapters/studies presented and discussed in this thesis. I was involved in the conception, design, and analysis of all studies. All participants were recruited, consented, and tested by me. For Chapter 2, Experiments 1 and 2 I set up the pain model and performed psychophysical assessments. For Chapter 3 I wrote all programming and conducted all assessment of participants. Additionally, all the statistical analysis in this thesis was conducted by me. Finally, I have written all the chapters of this thesis which have been reviewed by my supervisors, Dr David Moore, Professors Francis McGlone, and Dr Helen Poole.

For Chapter 2, Experiment 2, myself, Sarah Vaughan, and Dr David Moore conceived of the study and participated in its design. I, Sarah Vaughan coordinated the study, drafted the manuscript, protocol, ethical application, performed the measurements, collected the data, and ran the statistical analysis. Dr David Moore, Professor Francis McGlone and Dr Helen Poole contributed to the manuscript. All authors read and approved the final manuscript.

For the systematic review, myself Sarah Vaughan, Dr David Moore, Dr Helen Poole and Dr Mark Forshaw and Professor Francis McGlone conceived the study. I, Sarah Vaughan coordinated the study, collected the data, ran analysis, and drafted the manuscript. Dr David Moore, Professor Francis McGlone, Dr Helen Poole, Dr Mark Forshaw, Dr Michelle Failla and Dr Carissa Cascio contributed to the manuscript and all authors approved the final manuscript.

Abbreviations Used in the Thesis

AD – Action Descriptor

ADI-R – Autism Diagnostic Interview - Revised

ADOS – Autism Diagnostic Observational Schedule

ANOVA – Analysis of Variance

AQ – Autism Quotient

ASD – Autism Spectrum Disorder

ASI – Anxiety Sensitivity Index

ATS - Advanced Thermal Stimulator

AU – Action Unit

CDT – Cold Detection Threshold

CFCS – Child Facial Coding System

CI – Confidence Interval

CNS – Central Nervous System

CPM – Conditioned Pain Modulation

CPT – Cold Pain Threshold

CPTOL – Cold Pressor Tolerance

DD – Developmental Delay

DFNS - The German Research Network on Neuropathic Pain

DISCO – Diagnostic Interview for Social and Communication Disorders

DMA – Dynamic Mechanical Allodynia

DSM-5 – Diagnostic Statistical Manual 5

EMG – Electromyography

FACS – Facial Action Coding System

FP – Fear of Pain

GDPR – General Data Protection Regulation

GED-DI - Grille d'Evaluation de la Douleur-Deficince Intellectuelle

HPT – Heat Pain Threshold

HTOL – Heat Tolerance

HV – High Voltage

IASP – International Association for the Study of Pain

ICC – Interclass Correlations

IQ – Intelligence Quotient

IRR – Inter-Rater Reliability

MANOVA – Multivariate Analysis of Variance

MAX – Maximally Discriminative Facial Coding System

MDT – Mechanical Detection Threshold

MPS – Mechanical Pain Sensitivity

NCAPC – Non-Communicating Adults Pain Checklist

NCCPC – Non-communicating Child Pain Checklist

NRS – Numeric Pain Scale

PASS – Pain Anxiety Symptoms Scale

PCS – Pain Catastrophizing Scale

PDD-NOS – Pervasive Developmental Disorder – Not Otherwise Specified

PHS – Paradoxical Heat Sensations

PL-BPRS - Pre-linguistic Behavioural Pain Reactivity Scale

PPT – Pressure Pain Threshold

QST – Quantitative Sensory Testing

RBS-R – Restrictive Behaviour Scale - Revised

RRBs – Restrictive Repetitive Behaviours

SED – Socioeconomic Disadvantage

SIB – Self-Injurious Behaviour

TAS-20 – Toronto Alexithymia Scale

TSK – Tampa Scale of Kinesiophobia

TSL – Thermal Sensory Limen

VAS – Visual Analogue Scale

VDT – Vibration Detection Threshold

VJT – Volitional Joystick Task

WDT – Warm Detection Threshold

WUR – Wind-up Ratio

Choice of Autism Language

Throughout this thesis identity first language has been adopted, to reflect the research which highlights a large majority of autistic people and their families showing a preference for identity first language. However, I have chosen autistic individuals as the term to be used rather than autistic people due to its appropriateness in the context and style of writing. For example, to suggest that autistic people have aversions to touch, is precisely the notion we do not want to fuel. 'Autistic individuals' recognises that some individuals do indeed have these aversions, but it is not always applicable to the autism population. Secondly, I acknowledge that there is some discussion around either using the term Autism rather than Autism Spectrum Disorder, and that many advocacy sites and research use Autism. However, since the participants in this thesis were diagnosed in line with the DSM, the adoption of Autism Spectrum Disorder has been used in line with the most recent revision of the DSM.

Abstract

Evidence to date of altered pain processing in Autism Spectrum Disorder (ASD) is largely reliant on case evidence and observations. The evidence suggests a hypo sensitivity to pain which is emphasised by the inclusion of this as a criterion in the DSM-5. However, this evidence has also yielded contradictory findings on hypersensitivity to pain and suffers with methodological flaws. The aim of this thesis was to experimentally investigate pain in ASD using robust psychophysical pain induction methods to expand our understanding of where in the pain process differences occurred that could account for the altered behaviours observed in the anecdotal evidence.

Experiments 1 and 2 in Chapter 2 examined the processing of pain in people with autistic traits and those clinically diagnosed with ASD, using a comprehensive psychophysical test battery. Detection and pain thresholds were obtained for thermal and mechanical stimuli including vibration and pressure. Additional tests included a cold pressor, (Experiments 1 and 2). No consistent Quantitative Sensory Testing (QST) pattern of difference in relation to autistic trait severity or clinically diagnosed ASD, was observed. The Mechanical Detection Threshold exceeded that of a normal distribution of healthy individuals, as established by The German Research Network on Neuropathic Pain normative values (Backonja et al., 2013; Rolke, Baron, et al., 2006) for both autistic traits (Experiment 1) and clinically diagnosed ASD (Experiment 2) and differed to controls. Dynamic mechanical allodynia and paradoxical heat sensation were reported in a number of those with high autistic trait severity (Experiment 1) or clinically diagnosed ASD (Experiment 2), which does not typically occur in individuals otherwise considered healthy. Notably, there were a larger number of QST scores that fell outside the normal distribution (n = 48) in the clinically diagnosed ASD group (Experiment 2). A greater number of autistic individuals compared to controls, were found to show atypical patterns of pain response (n = 10). Indicating that there

488 is a heterogeneity of pain response in ASD and that there may be subtypes with different pain
489 responses.

490 Experiment 3, Chapter 3, utilised a volitional joystick task to determine if there was a
491 greater attenuation of pain avoidance behaviours by a valued reward in ASD. Individuals
492 clinically diagnosed with ASD and controls, moved a joystick towards a target that resulted
493 in the delivery of a nociceptive stimulus, which on 50% of occasions was paired with a
494 reward. During choice-trials participants opted to make a safe movement (i.e., an opposing
495 movement to the movement paired with pain in which there is no pain stimulus) or to make a
496 movement towards a monetary reward whilst receiving a nociceptive stimulus. Reaction
497 times were obtained for movements, as well as the number of choice trails. The ASD group
498 were no different to controls at completing a painful yet rewarding movement and they also
499 chose to negate the pain to receive a reward to the same degree as controls, suggesting that
500 the ASD group's fear avoidance and pain motivation processing is no different to controls.

501 Experiment 4, Chapter 4, utilised the Facial Action Coding System and the Non-
502 Communicating Adults Pain Checklist to code facial and behavioural responses to pain. The
503 aim was to determine if the communication of pain in ASD differed to controls, or if there
504 was a set of ASD specific pain behaviours. Participants were videoed during a cold pressor
505 task and thermal heat stimuli (6 warm but not painful, 6 moderately painful, and 6 very
506 painful). Painful facial expressions for cold and hot thermal stimuli were similar between
507 the ASD group and controls. The ASD group showed expressions in the lower oblique
508 cluster (comprised of muscles that pull the skin of the face upward at an oblique angle) more
509 frequently. These expressions were also observed at a greater intensity in comparison to
510 controls. In particular, Nasolabial Furrow Deepener and Lip Corner Puller occurred more
511 frequently and at a greater intensity in the ASD group compared to controls. Controls were
512 also more likely to show a neutral expression compared to the ASD group, indicating a

masking mechanism is being employed by controls in the social context. It is possible that the social contagion or mimicry of expressions is focussed on the lower facial regions and therefore pain expression develops more so in this region for autistic individuals.

Taken together, the findings from this thesis point towards greater intra-individual differences in the ASD group compared to controls, showing that there may be sub-groups in the autistic population who have altered pain experiences, or for whom pain expression might be more nuanced. Importantly, the results presented here do not support the DSM-5's statement that an absence of the ability to feel pain is a defining feature of ASD.

Chapter 1. Theoretical Background

Chapter 1. General Introduction

1.1 Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a heterogenous, pervasive, lifelong neurodevelopmental disorder. The DSM-5 (5th ed., APA, 2013) aggregates the formerly separate autism subgroups: Autism, Asperger syndrome, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), into one broad spectrum disorder. There are two main clusters of behaviour:

1. persistent deficits in social communication and social interaction across multiple contexts: social emotional reciprocity, non-verbal communicative behaviours and developing, maintaining, and understanding relationships (APA, 2013). The social interactions range from self-imposed social isolation (Klin et al., 2000) to somewhat engaged but inappropriate social behaviour, where typically eye contact is avoided (Dalton et al., 2005; Pelphrey et al., 2002) or there is a tendency to respond inappropriately in conversation (APA, 2013). Deficits in receptive communication are present, with individuals demonstrating reduced attention, poor understanding of non-verbal language and difficulties with non-literal language (Hobson, 2012; Tager-Flusberg, 1999; Vance & Wells, 1994). Impairment in the social use of language is therefore a common behaviour witnessed.
2. restrictive, repetitive patterns of behaviour, interests, and activities cluster. Such behaviours can take a range of forms, from compulsive insistence on daily routines to an intense focus on specific, narrow topics of interest (Ozand et al., 2003). A change to established routines can lead to overtly expressive behaviours, such as meltdowns and resistance, including anger attacks

(Flectcher-Watson & Happe, 2019; Frith & Happe, 1994; Happé & Frith, 1996; Ozand et al., 2003), as well as self-injurious behaviour patterns, including self-biting, head banging, to self-soothing patterns such as rocking (Happé & Frith, 1996; Ross-Russell & Sloan, 2005). A specific feature in this cluster is that of "hyper- or hypo-reactivity to sensory input", where the DSM-5 gives the specific example of "apparent indifference to pain/temperature, adverse response to specific […] textures, excessive […] touching of objects" (APA, 2013). Such sensory processing abnormalities have been a feature of ASD clinical descriptions, from the original independent seminal reports by Asperger (Asperger, 1944) and Kanner (Kanner, 1943) to first person accounts from case reports (Dunn et al., 2002; Grandin, 1992; Marco et al., 2011). Research focussing on sensory processing abnormalities reports sensory processing difficulties spanning all the senses: taste, touch, smell, audition, and vision, for all ages and all levels of ASD symptom severity (for review see Baum et al., (2015); Marco et al., (2011)). Additionally, the distress caused by sensory stimuli has also been shown to cause self-injurious and aggressive behaviour in those unable to communicate this burden (Duerden et al., 2014; Handen et al., 2018; Melia et al., 2015; Richards et al., 2016; Vandewalle & Melia, 2021). While sensory hyper- and hypo-responsiveness are not unique to ASD, they appear to be more prevalent in this population than in other developmental disabilities (Baranek, 2002; Ben-Sasson et al., 2009; Leekam et al., 2007). However, in comparison, pain in ASD is relatively poorly understood.

1.2 Pain Definition

Pain is more than just the result of sensory processing; it is a complex conscious experience. The definition of pain acknowledges that it is a multifaceted, distressing experience associated with actual or potential tissue damage; with sensory, emotional, cognitive and social components (International Assosiation for the Study of Pain, 2020; Williams & Craig, 2016). Therefore, the definition recognises not only the nociceptive threat of tissue damage but the wider experiential aspects (Eccleston, 2013). In general, the more intense the noxious stimulus is, the more unpleasant it is (Miron et al., 1989). Sensory information about a noxious stimulus, such as a burning hot temperature, is transmitted centrally through special classes of nociceptor afferents (Treede, 2006). Nociception is most often the cause of pain (Iannetti & Mouraux, 2010), however, there is no direct relationship between nociception and experience of pain (Merskey, 1986), and the two may occur separately (Loeser & Treede, 2008). This definition also reflects the difficulty one person would have in inferring another person's experience. Therefore, what may be perceived as painful in one individual (for example, the adverse response to texture mentioned in the DSM) may not be painful in another.

Pain can also be categorised in several ways, one of which is to separate it into acute and chronic. Acute pain can be defined as the predicted physiological response to an adverse stimulus (Carr & Goudas, 1999), whilst chronic pain is that which persists or recurs for several months (Treede et al., 2019). Chronic pain can be further split into categories based on the damage it causes, such as neuropathic pain, which is thought to be the result of lesion or disease of the somatosensory system (St John Smith, 2017). However, acute pain has been associated with new tissue injury that can last for several months (*Classification of Chronic Pain, Second Edition (Revised) | International Association for the Study of Pain (IASP)*,

retrieved 2021) and therefore could be viewed as the initiation of a persistent nociceptive and behavioural cascade triggered by tissue damage (Carr & Goudas, 1999).

1.3 Neural Mechanisms of Nociception and Pain

Different types of specialised peripheral sensory neurons, known as nociceptors, alert us to potentially damaging stimuli at the skin (Dubin & Patapoutian, 2010). Nociceptive afferents are classified based on conduction velocities, threshold, and sensitivity to stimuli type, namely thermal, mechanical, and chemical modalities. A-fibre nociceptors are predominantly heat or mechanosensitive, are myelinated, with an onset of 5-50m/s. Whilst C-fibre nociceptors are responsive to heat and are unmyelinated with an onset of 0.4-1.4m/s (Cain et al., 2001; Lewin & Moshourab, 2004). Noxious stimuli activate an ion channel on the nociceptor which depolarises it producing a potential. If the potential has significant magnitude to reach the activation threshold for voltage-gated Na+ channels, it triggers an action potential (St. John Smith, 2017). Nociceptor activity does not per se lead to perceptions of pain as mentioned above, although it most often is the cause. The latter requiring peripheral information to reach higher centres and normally depends on the frequency of the action potentials in primary afferents, temporal summation (the phenomenon in which repeated and equal intensity stimuli cause an increase in the pain experienced), pre- and post-synaptic signals and central influences (Dubin & Patapoutian, 2010; Willis & Coggeshall, 2004). When an action potential is triggered, the signal follows a direct axonal pathway from the periphery to the spinal cord (Amir & Devor, 2003). The central axon carrying the signal enters the spinal cord and sprouts branches that innervate multiple spinal segments and terminate in the dorsal horn on relay neurons and local interneurons important for signal modification (Basbaum et al., 2009; Millan, 1999). Projections from here include the medulla, mesencephalon, and the thalamus, which in turn project to somatosensory and

anterior cingulate cortices, all of which comprise the pain neuromatrix, although this matrix may not be specific for pain (Iannetti & Mouraux, 2010). Together this drives both sensory-discriminative and affective-cognitive aspects of pain (Iggo, 1977; Millan, 1999). These interneurons, both inhibitory and excitatory, as well as descending inhibitory and facilitatory pathways, modulate the transmission of the nociceptive signals thus contributing both to the prioritisation or inhibition of pain (Heinricher et al., 2009).

1.4 Mediators and Moderators of Pain

As the pain definition proposes, pain also incorporates social, emotional, and cognitive factors (International Assosiation for the Study of Pain, 2020). Research has recognised that there are a variety of pain moderators and mediators, which are part of how pain will be experienced and evaluated, and therefore responded to. In terms of emotional factors, much research has focussed on anxiety and fear, without making a clear distinction between the two, instead focussing on pain-related fear used to denote both the reaction to current pain and anticipatory anxiety (see Peters, (2015) for a review). Pain related fear has been shown to increase pain sensitivity and exaggerate the pain experience (George et al., 2006; Hirsh et al., 2008; Roelofs et al., 2005). When distinguishing between anxiety and pain related fear, Rhudy and Meagher (2000) found fear to reduce pain reactivity, while anxiety led to increased reactivity as measured by withdrawal reflex latencies to radiant heat stimuli. Anxiety has also been implicated in pain via the fear-avoidance model of chronic pain (Botvinick & Braver, 2015; Crombez, Eccleston, Van Damme, et al., 2012; Van Damme et al., 2008, 2010). The model proposes that fear of pain and reinjury hampers recovery from acute pain because anticipatory anxiety motivates avoidance behaviour. However, fear of pain is also a predictor of acute cold pressor pain thresholds (Hirsh et al., 2008), as well as acting as a mediator in sex differences in thermal pain thresholds (Horn et al., 2014). Fear of

pain, above and beyond anxiety, has also been shown to predict pain intensity and unpleasantness ratings at threshold and tolerance (Horn et al., 2014; Rainville et al., 2005). Pain related fear and anxiety, whether distinct or not, therefore inflate the perceptual experience of a nociceptive stimulus and are implicated in the chronification of pain. Furthermore, clinically relevant anxiety and depression have purported similar effects (see Thompson et al., (2016) for a review). Depressive mood is also related to a reduced pain tolerance and increased pain unpleasantness (Loggia et al., 2008).

In terms of cognitive factors, those most frequently researched are attention, expectancy, and appraisal in the form of catastrophizing. Pain catastrophizing is the tendency to magnify the threat value (appraisal) of actual or anticipated pain experience, paired with exaggerated negative cognitive schemas (expectancy) and inability to divert attention away from pain (attention; Gatchel et al., (2007)). Therefore, the core quality of attention is the importance of information processing in the brain, such that there is an ability to adapt which cognitive resources are focused on certain aspects of the environment and not others (Lindsay, 2020). Whilst appraisal is the assessment of the threat value or interpretation of a stimulus, and expectancy is the cognitions regarding the probability of future experiences (Leung, 2012; Quartana et al., 2009).

Attention and nociception are thought to have a bidirectional relationship with each other (Legrain et al., 2012; Torta et al., 2017). Pain can capture attention, particularly if it is novel or threatening, with the purpose of promoting action (Legrain et al., 2012; Peters, 2015). Therefore, since pain is motivationally relevant, this draw of cognitive resources can interfere with other tasks (Crombez et al., 1994). On the other hand, directing attention towards pain is thought to increase the perceived intensity, whilst drawing it away can lead to a less intense experience (Crombez et al., 2005). Numerous studies have shown distraction,

for example via a competing task, diminishes pain (Claes et al., 2014; Legrain et al., 2012; Van Damme et al., 2010, 2012). Heightened attention, i.e., hypervigilance, has also been implied in the transition from acute to chronic pain (Vlaeyen & Linton, 2012), with individuals who are highly fearful of pain, and whose main goal is avoidance, becoming hypervigilant (Crombez et al., 2005), thereby showing the complexity and connection between both emotional and cognitive factors. Pain catastrophizing is another cognitive factor that has connections and confounds with emotional factors, namely fear of pain (Hirsh et al., 2008). This is because it is thought to encompass several aspects of negative thinking including exaggeration of threat value, rumination and helplessness (Sullivan et al., 2001) which are also associated with anxiety (Peters, 2015). Pain catastrophizing has much of the same associations with pain intensity and unpleasantness as the aforementioned factors. In particular, an increase in pain sensitivity (Quartana et al., 2009; Sullivan et al., 2001), when paired with fear of pain, significantly predicted pain intensity ratings (George et al., 2006; Hirsh et al., 2008). There are also aspects of expectancy in pain catastrophizing, i.e., the definition incorporates the concept that pain may not disappear. Expectations about a painful event or nociceptive stimulus have been reported to alter the perceived intensity. For example, expecting low pain decreases pain perception and expecting more pain increases it (Benedetti et al., 2003; Hird et al., 2019; Price et al., 1999; Tracey, 2010; Zaman et al., 2018). Of particular note, is the finding that a previously judged innocuous stimulus could be perceived as a painful stimulus via painful expectations (Colloca & Benedetti, 2009). These factors are also not separate and distinct from one another, there are complex relationships and mechanisms involved. For example, pain catastrophizing and pain related fear may lead to attention to pain (see Peters, 2015 for a review).

In terms of social factors, the most frequently researched is that of social support, social exclusion, and socioeconomic disadvantage (SED). Social support is thought to have a

beneficial impact on pain experience. Having the support of a spouse or other partner during painful episodes leads to decreased pain reports in the clinical setting. For example, during labour, the presence of a birthing partner leads to decreased pain reports and a reduction in pain medication (Cano et al., 2004; Lee et al., 2016; López-Martínez et al., 2008). In the experimental setting, this reduction in intensity and tolerance has been replicated, whether the social support comes from interacting with someone (Brown et al., 2003; Edwards et al., 2017; Goldstein et al., 2016; Jackson et al., 2005; Roberts et al., 2015; Vlaeyen et al., 2009) or reminding participants about social connections (Eisenberger et al., 2011; Master et al., 2009; Shaygan et al., 2017; Younger et al., 2010). Social isolation and exclusion have been found to increase pain intensity (DeWall & Baumeister, 2006; Dorner et al., 2011; MacDonald & Leary, 2005), with worsening pain in those with less social support. The relationship between SED and risk for chronic pain, and pain conditions such as sciatica, ulcer and neuropathic pain, is constant regardless of the definition of SED (Heliövaara et al., 1991; Levenstein & Kaplan, 1998; Poleshuck & Green, 2008; Torrance et al., 2006). Findings show increased risk of these conditions when SED is high. As well as lower material status being significantly associated with lower pain tolerance (Miljković et al., 2014). Importantly, these factors do not appear to impact pain in isolation of each other, for example, greater material status over social exclusion diminished pain intensity ratings (Zhou et al., 2009). Previous studies have also demonstrated that pain is modulated by associations learned through reinforcement. Stimuli associated with intense pain subsequently becomes more painful when paired with social stimuli suggesting that others have experienced high pain (Atlas et al., 2010; Koban & Wager, 2016). This evidence also shows that expectancies have a role to play in this relationship, showing a complex interaction with cognitive mediators such as expectancies or learning (Koban & Wager, 2016). Interactions between social modulation and pain are also reported for stress and anxiety. Wherein a buffering

effect on pain occurs through social circumstances acting as a psychological safety signal to reduce stress and anxiety around pain (Che et al., 2018). Furthermore, experimental evidence of empathy for pain has shown that observing another person experiencing pain relief is also sufficient to serve as a reinforcer, and shape pain perception (Colloca & Benedetti, 2009; Goldstein et al., 2016; Goubert et al., 2011), highlighting further complex interactions between social, cognitive, and emotional factors and pain. Therefore, these factors can also act as confounds and so must be considered when measuring the pain experience.

1.5 Pain Communication

In order to communicate subjective pain experience to the social environment a range of behaviours are employed, including body gestures, verbal, and non-verbal cues, such as facial expression (Craig, 2015; Craig et al., 2001; Mogil, 2015; Walsh et al., 2014). Verbal communication of pain is the most typical form of expression (Fields, 1999; Zaccagnino & Nedeljkovic, 2017) for those able to verbally communicate their pain experience. Pain communications of this type are complex because they require a shared language, with cultural contextual social factors, in order for the symbols used to describe pain to be comprehended and understood by the receiver (Hadjistavropoulos, et al., 2011; Peacock & Patel, 2008; Schiefenhövel, 1995). However, delayed, or total lack of language development, or of discrepant comprehension of language and the social use of language, may impede the development of pain-specific language (Davidson & Ellis Weismer, 2017; Mitchell et al., 2006). In such cases, body gestures and nonverbal cues are more heavily relied upon. There is also inherent risk of misunderstanding pain, even in those considered healthy and able to communicate their pain (Rowbotham et al., 2012) and so verbal communication of pain is supplemented by body gestures and other non-verbal cues. For example, painful facial expressions are thought to be especially indicative of the emotional component of pain (Kunz

et al., 2012), and they have been found to be a major determinant of observer's judgements of pain (Breau et al., 2007; Breau et al., 2003; Breau et al., 2002; LaChapelle et al., 1999; McGrath et al., 2008). Research investigating non-verbal pain behaviours have shown that these behaviours correspond to the timing of painful events and that the magnitude of expression can be quantified (Breau et al., 2007; Breau et al., 2003; Breau et al., 2002; Izard et al., 1980; LaChapelle et al., 1999; McGrath et al., 2008; Oberlander et al., 1999), suggesting non-verbal modes of communication are reliable in decoding pain experience (Messmer et al., 2008). The goal of these behaviours is generally thought of as an external signal that invokes help from a second person, usually a carer or parent (Schott, 2004; Sullivan, 1995). This behavioural activity of pain then permits observer inference (Prkachin, 2009; Riddell et al., 2013; Schiavenato & Craig, 2010).

1.6 Pain Measurement

Ideally, pain measures would provide an easily interpretable and directly transferable metric in the same way that for example, blood pressure and cholesterol levels do (Kroenke, 2018), however, since the experience of pain is poorly related to the nature and magnitude of tissue damage and is both complex, and subjective (Chou et al., 2009; Loeser, 2012), the ideal metric is currently unobtainable. Therefore, the current gold standard for pain reporting is self-report, which represents the internal percept of a stimulus. Clinically, pain scales are typically simple unidimensional methods that assess pain intensity and unpleasantness (magnitude of pain experienced and the magnitude of the experience, respectively; Fields, (1999); Zaccagnino & Nedeljkovic, (2017)). They are however adaptable, and so can be used to measure a particular construct of pain, for example, ability to endure a pain, quality of pain and impact (Zaccagnino & Nedeljkovic, 2017).

The most frequently used of these pain scales are the numeric rating scale (NRS), the visual analogue scale (VAS) and the faces pain scale (Wong & Baker, 2001). Although these are different measures, they are visually analogous in their question presentation. For example, a typical NRS consists of a scale from zero (no pain) to ten (worst pain imaginable) and the VAS consists of a 10cm line with no pain at one end and worst possible pain at the other. Although these measures are used to compare pain between groups (Backonja et al., 2013; Rolke, Magerl, et al., 2006) others have criticized this utility arguing that the responses are only relative to that individual (Zaccagnino & Nedeljkovic, 2017), because what someone might perceive as the worst pain imaginable can differ. However, these measures all have good reliability and consistency (Downie et al., 1978; Ferraz et al., 1990; Woodforde & Merskey, 1972). Of note here is that self-report requires a communicative ability to comprehend and respond to these pain scales.

For those with communication difficulties, assessing pain behaviours may be more suitable (Katz & Melzack, 1999). Examples of pain behaviours include saying "ouch", grimacing, limping, rubbing, or soothing the location. From the behaviours an inference can be made of nociception, pain and the suffering experienced (Loeser & Melzack, (1999), see section 1.4). This can be achieved with behaviour checklists, behaviour-rating scales or those that measure a specific aspect such as facial expressions. A behaviour checklist provides a list of behaviours that are then observed as being present or absent. A scale applies an intensity rating to listed behaviours, and those that incorporate facial expressions do both (Donate et al., 1999; Ekman, 1992; Katz & Melzack, 1999; von Baeyer & Spagrud, 2007). Coding schemes should be both exclusive and exhaustive, that is to say that each behaviour can only be assigned to one code, and that there is a code for every behaviour (Chorney et al., 2015). This helps to foster reliability and validity when coding is reliant on a degree of judgment. Such approaches have flexibility in that a researcher can develop a coding scheme

through operationally defining what is important to the research question being asked and the sample it is observing. Observational schemes can also be micro or macro. Micro-coding captures behaviours at a very specific level (Bell & Bell, 1989) and allows for a specificity that macro coding (larger interactions of behaviours) does not (Chorney et al., 2015). An example of a micro-coding scheme is the Facial Action Coding System (FACS). This is a system whereby facial expressions are coded and is thought to be a more objective observational tool as movements and expressions are based on the anatomical connections and movements of facial muscles (Ekman, 1992). However, these tools are time consuming not only in their creation but their application (Zaccagnino & Nedeljkovic, 2017).

1.7 Pain Induction Methods

Psychophysics is the analysis of perceptual processes via investigating the effect a stimulus has on behaviour and experience by varying physical properties of the stimulus (Bruce et al., 2003; Read, 2015). Psychophysics also refers to a set of pain induction methods that can be applied to the somatosensory system and deals with the relationship between physical stimuli and their subjective correlates or percept's (Kingdom & Prins, 2016; Tursky et al., 1982). A large number of combinations of stimulus and response methods are available which allows for flexibility depending on the goal of the experiment, especially as choice is not restricted to one modality (Gracely, 2013). A combination of modalities; thermal, mechanical and deep pain (pressure and vibration) can therefore be tested, and many of these methods have been built into test procedures (Backonja et al., 2013; Rolke, Magerl, et al., 2006). Generally speaking, the psychophysical approach incorporates single point measures of pain such as threshold and tolerance (Gracely, 2013).

Perceptual threshold refers to the minimal amount of stimulation that evokes a report e.g., pain (Gracely, 2013). Individuals identify that point which separates painful from non-

painful experience (Chapman et al., 1985). Two thresholds can be measured by applying a stimulus to the skin: (1) sensation threshold, the point at which a stimulus is first detected, sometimes termed the detection threshold; and (2) pain perception threshold (Melzack et al., 1982). Those with a high threshold require greater stimulus input in order to report pain, compared to those with a lower threshold, who require far less input (Gracely, 2013). Tolerance is the maximum level of stimulus intensity that the individual reports as being able to experience (Chapman et al., 1985) and is distinct from threshold (the point at which pain begins to be felt). A measure of threshold and tolerance comprises of the sensitivity of the subject to the stimulus and the subject reporting that the stimulus was painful (Irwin & Whitehead, 1991). Therefore, assessing the somatosensory system from receptor to cortex, including the perceptual component of pain (see section 1.8 for overview).

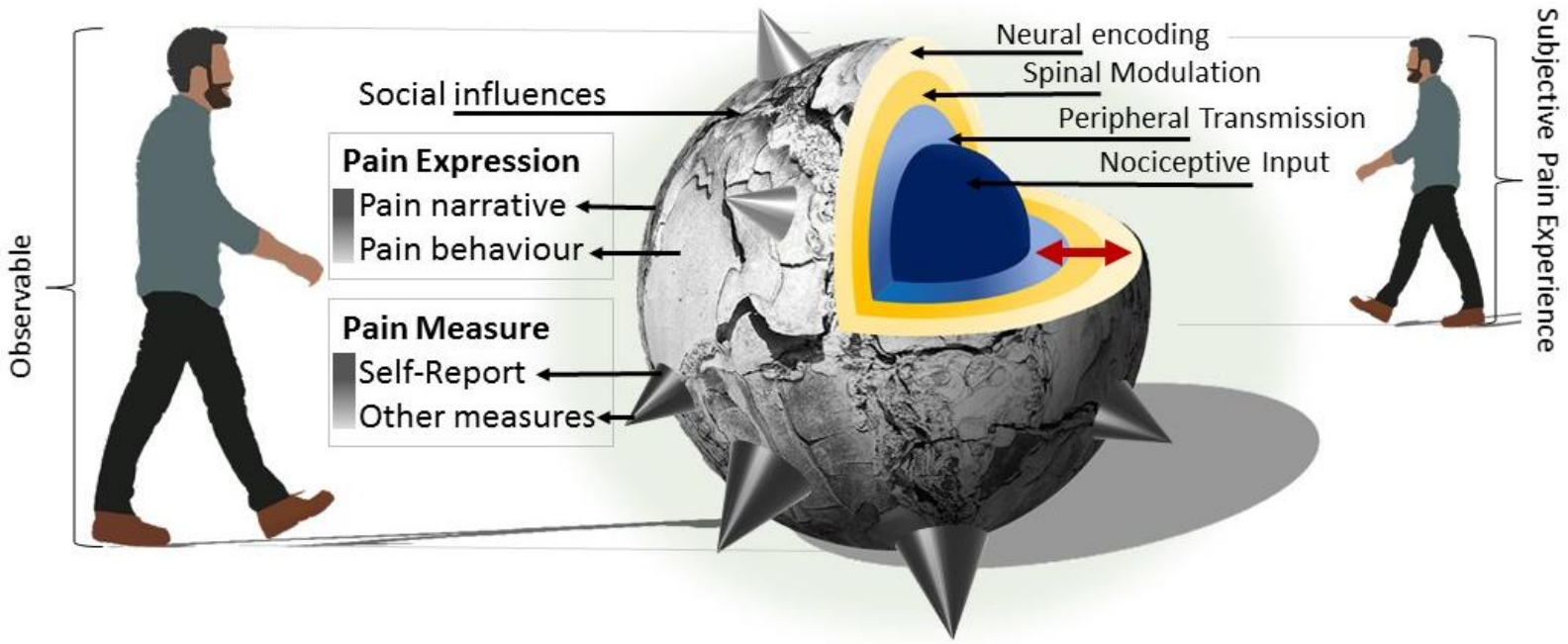
In order to determine threshold and tolerance levels, typical psychophysical experiments use two methods: the method of limits or the method of levels. Method of limits consists of presenting a stimulus in ascending increments until pain is reported or descending until pain ceases (Edens & Gil, 1995), a strength of which is that it is a reaction time inclusive method (Moloney et al., 2012). Method of adjustment or levels consists of subjects adjusting the stimulation to the just painful level (Edens & Gil, 1995). Its strength is in being a reaction time exclusive method (Moloney et al., 2012). For example, thermal modalities can be tested using either method of limits or method of levels, where either a slowly increasing temperature is applied until a participant defines pain, or a set of specific temperatures are applied, and ratings given to each. Both these methods have their strengths and utility, however, there are limitations. Notably, they are more subjective in nature than determination of a sensory threshold where the subject chooses between the presence or absence of a pain (Gracely, 2013), although a subjective approach to pain may be exactly what is necessary for an inherently subjective experience.

1.8 A Conceptual Model of Pain

The evidence presented above, highlights that pain is a dynamic interaction among the biological, psychological, and social. Therefore, a biopsychosocial model is the most heuristic approach to conceptualising the pain experience. Loeser, (1980), proposed a four-dimensional biopsychosocial model for pain, which included nociception, pain, suffering and pain behaviour. In this model, in line with the current understanding, nociception is a peripheral event that typically leads to pain and so is placed at the core of the model, with pain sitting one level up. Since this link can be modulated or mediated by surgical, pharmacological, or psychological means as presented, pain is listed as separate to nociception, highlighting it as a feature of the spinal cord and the brain. The affective aspect engendered by pain then becomes another layer in the model, with the outermost layer then the behavioural outputs of these internal events. However, this model oversimplifies the complexity of the pain experience and fails to incorporate external social influences that drive behaviour as well as ways in which pain can be assessed, despite encouraging a multidimensional approach to assessment and treatment of pain. For this reason, Wideman et al., (2019) have proposed the Multimodal Assessment Model of Pain. However, this simplifies the earlier levels proposed by Loeser (1980) into one internal subjective experience, although, its strength is in recognising, the environment, pain expression and pain measures. Therefore, Figure 1 presents an adapted version of both Loeser and Wideman's models, recognising the strength and utility these models present in terms of a framework on which to base pain research, as well as addressing their respective limitations. This model can be used to show how subtle differences at various points in the system, could result in differences in the pain experience.

Figure 1.

The Loeser/Wideman Integrated Multimodal Model of Pain (The IMMP).



Note: This 3-dimensional view emphasizes the subjective pain experience and the observable person perspectives. The core of the model and the subterranean layers highlight the internal unobservable mechanisms that are involved in the pain experience. Nociception is at the core to reflect that nociception typically results in pain, and the peripheral, spinal, and neural mechanisms involved. However, since pain can occur without nociception, and that there is also a top-down modulation of pain, the red arrow on the subterranean layers, indicates that there are bi-directional processes occurring through these layers. The neural level represents the motivational-affective, cognitive evaluative and sensory discriminative functioning. This 3D view also emphasizes how pain experience is a function of the whole person, who is influenced by environmental and contextual factors (indicated by the green haze) including social influences (indicated by the textured cracked surface, cracks indicating that social, environmental, and contextual factors seep through to the internal). The textured uneven surface of pain expression represents the collection of words and behaviours that any individual may use to express pain. This contrasts with the smooth surface of pain measures (cones), which require expressions of pain to be translated into metrics. Cone size represents the relative ability of different pain measures to quantify different aspects of pain expression; measures with relatively larger cones indicate that they address a broader scope of pain expression. Gradients are used to depict the intimate link between the pain narrative and pain behaviour. This model integrates aspects from both Loeser (1980) and Wideman et al., (2019) models into one comprehensive biopsychosocial model. All images, with the exception of the walking man (creative commons licencing: https://cdn.pixabay.com/photo/2017/08/17/15/32/walking-2651721_640.png), belong to the author of this thesis, having been created, edited and adapted by the author (SV) for the purposes of generating this diagram.

1.9 Risk of Pain and Painful Comorbid Conditions in ASD

Alongside the sensory and psychiatric comorbidities, such as Obsessive Compulsive Disorder (Meier et al., 2015), autistic individuals often present with a range of comorbidities, some of which are linked to altered pain processing or are painful conditions themselves, such as headaches or joint hypermobility (Baeza-Velasco et al., 2018; Victorio, 2014) or increase the likelihood of injury (Lee et al., 2000). For example, autistic individuals are thought to be at a disproportional risk of developing other psychiatric conditions such as depression and anxiety (see Hollocks et al., 2019 for review), both of which research has found to have a bidirectional relationship with altered pain behaviours (for review, see Thompson et al., 2016). Sleep disturbances, a common clinical feature of ASD (Deliens et al., 2015; Hering et al., 1999), are also linked to a greater vulnerability to pain (see Finan et al., (2013) for review). Although this needs to be more clearly considered in ASD populations, evidence does suggest that those with ASD diagnosis are more likely to be susceptible to experiencing pain if sleep disturbances are experienced (Deliens et al., 2015). Research has also demonstrated that autistic individuals are at high risk for developing epilepsy, with the risk being highest in those with intellectual disability (Bozzi et al., 2018; Scott & Tuchman, 2016; Thomas et al., 2017). One hypothesis to explain this co-morbidity postulates that the neurodevelopmental deficits lead to changes in networks and neurotransmitters (see review Bozzi et al., (2018)) which are also involved in the mediation and perception of pain (Enna & McCarson, 2006). Additionally, an alteration in consciousness or loss of motor control that is symptomatic of a seizure can lead to accidental injuries, such as falls (Camfield & Camfield, 2015), but additionally, the seizure itself may be painful (Young & Blume, 1983). Above and beyond motor difficulties in epilepsy leading to injury, those with gait issues (gross motor skills) are at a greater risk of injury (Pirker &

Katzenschlager, 2017). In ASD, fine motor skills, rather than gross-motor skills, have been linked with increased visits to hospitals for injuries (Myhre et al., 2012) and motor difficulties are reported 87% of those with ASD (Bhat, 2020; Jain et al., 2014). Although research needs to establish whether autistic individuals are at greater risk of injury or painful experiences either due to epilepsy or motor skills, there is compelling evidence that they are at greater risk of painful experiences when epilepsy or motor skills problems are co-morbid.

1.10 Chronic Pain in ASD

Whether autistic individuals are likely to experience co-morbid chronic pain conditions has become the focus of several recent research studies. Clinical reports highlight case evidence of a comorbidity with rheumatic or generalised muscle and joint pain (Clarke, 2015; Lipsker, Bölte, et al., 2018; Loades, 2015), that according to reports meets the current criteria for chronic pain i.e., lasting longer than 3 months (International Assosiation for the Study of Pain, 2020). One case study highlights that the patient had suffered with chronic pain from the ages of 9 months (Lipsker, von Heijne, et al., 2018). Case evidence is also presented for the link to chronic abdominal pain, although in this particular example the link is tentative as the cases presented are undiagnosed individuals (Bursch et al., 2004); although there is evidence of core ASD features described by the clinician, and a referral for diagnosis is made. A further study showed that 25.8% of an ASD sample experienced chronic abdominal pain, which persisted at a one-year follow-up (Mazurek et al., 2014), highlighting that abdominal pain is common and persistent in this population. Although in other samples, this number is as low as 9% (Low Kapalu et al., 2018). Gastrointestinal issues are frequently described in the literature, and although generally considered in terms of an acute pain (lasting only as long as the gastrointestinal symptoms), the chronic nature of these issues support the connection of chronic pain to ASD (see for review McElhanon et al., 2014).

Surprisingly, although it might be expected that chronic pain be more widely considered within ASD, it is not a common finding. Understanding pain in this population is however, of utmost importance, highlighted by the cases of comorbidities presented above.

1.11 Autobiographical Accounts of Pain in ASD

Alongside the case evidence explored for sensory processing issues, there are a number of first-person accounts of pain in ASD. Touch and discriminative abilities are most frequently discussed wherein individuals report being unable to tolerate touch (Cesaroni & Garber, 1991; Elwin et al., 2012; Grandin, 1992). An additional first-hand account reports feeling overwhelmed by touch, specifically that touch "hurts" (Cesaroni & Garber, 1991 pg. 306) and reporting an aversion to this. Others discuss the idea that their nerves felt "supersensitive" to innocuous touch, even recognising that others would not find this painful (Grandin, 1992). This suggests that even the lightest of tactile experiences, that is modulated under typical circumstances by neurotypicals (i.e., receptor cells habituate to the feeling rapidly in those who are not characterised by autism or other neurologically atypical patterns), may be a great source of discomfort which is interpreted as pain for autistic individuals. More specifically, in the case of Jim, presented by Cesaroni and Garber, (1991), being touched caused confusion about the precise location and nature of the stimulus. Poor spatial discrimination in general (identifying the location of a stimulus) has been paired with pain. Specifically, identified sites of pain are remote in comparison to the site of injured tissue (Head, 1893; Marchettini, 1993; Mense, 1993). Since this ability relies on a functioning system of tactile afferents (Legrain et al., 2012; Liljencrantz et al., 2013; McGlone & Reilly, 2010; Schlereth et al., 2001), being confused about the location may point to an alteration in this system. In other instances, it is not a hyper-reactivity to stimuli that is present, as discussed above, but a hypo-reactivity, wherein the response to nociceptive inputs

do not appear to function typically. In one particular case, not only did the person not require additional layers of clothing in extreme cold weather, reporting that something was wrong with their "heating system" (pg. 236 Elwin et al., (2013)), but also that they did not react to temperature at all. This suggests that thermal response may be an altered modality. Research findings, using content analysis, report that touch is related to a hypersensitivity, where apprehension is paired with the stimulus and so the individual experiences a prolonged heightened state (Elwin et al., 2012, 2013). Alternatively, pain was frequently associated with a hypo-reactivity (Elwin et al., 2012, 2013). Research that synthesises these experiences frequently discusses the consequences of pain and the behavioural reactions they elicit. For example, a common theme is for repetitive routines to become more salient, or for other extreme behavioural responses such as stimming (behaviour consisting of repetitive actions or movements see Kapp et al., (2019)), crying, or meltdowns to occur (Elwin et al., 2012, 2013; O'Neill & Jones, 1997; Volkmar & Reichow, 2013). One particular case discusses how the individual felt that painful stimuli "could not be mastered" (Bemporad, 1979). Pain is a subjective experience (International Assosiation for the Study of Pain, 2020) and therefore understanding and establishing potential explanations for these experiences, in order to negate the resulting behavioural responses, is imperative.

1.12 Clinical Observation of Pain in ASD

Clinical observations have been used to describe pain responses in ASD, offering a more objective analysis and reducing bias which might occur in parent or self-report. Furthermore, observation is also thought to provide an insight into pain which can be difficult for those with an ASD diagnosis to communicate, particularly those who are non-communicative. In the initial report by Kanner (1943), the first descriptions of pain reactivity can be found, where patients diagnosed with ASD were tested using pinpricks. Opposing

reactions are described with one case finding the pinpricks painful and the second responding very differently, observed by Kanner as an indifference. Pinpricks are a standard test of mechanical pain, however in this instance, the lack of detail makes it difficult to determine whether it is an atypical response. For example, individuals without ASD find pinpricks painful and the typical weight at which this occurs is around 87mN (Rolke, Baron, et al., 2006). What is clear is that pain is observed in cases of ASD and being included in such an observation would suggest that it is atypical. Of the 11 cases described in Kanner's initial observations however, only 2 individuals are administered the pinprick test. Other early accounts further support this indifference to pain. Mahler (1952) gives an account of a child putting a hot cigarette lighter to her lip causing severe burning without a typical pain response for such an issue, suggesting an increase in pain thresholds. Later another case of a young boy was described in a similar instance, where the child placed their hand on a hot stove which resulted in burning that led to a loss of motor control and several reconstructive surgeries (Gillberg & Coleman, 2000). These case studies highlight potential consequences of an altered pain response. In other examples children are observed being able to withstand extreme cold temperatures, some naked and others with summer clothing on (Gillberg & Coleman, 2000; Wing, 1976; Wing, 1966).

Wing (1976;1966) summarises their observations into a scheme for diagnosis, which includes abnormal responses to pain, cold, and touch as well as paradoxical responses to stimuli. This is also the first instance where paradoxical sensations are discussed in reference to ASD. This observation of pain response being a core clinical feature is supported by Gillberg and Coleman, (2000) who report that all children with a diagnosis of ASD at an early age have abnormal responses to sensory stimuli. They additionally observe pleasure being derived from instances that would typically be painful. In one example a boy bites the back of his hand. This is a recurring theme in a later case described by Bursch et al., (2004)

where “Tony” is observed as deriving pleasure from tightening a belt to a point at which others would find painful. There is also the recurrence of contradictory responses, as both are reported as suffering from chronic pain. Clarke (2015) observed two similar opposing pain responses as does Lipsker et al., (2018). In this case extreme pain was witnessed after the resultant cause had been treated alongside other wounds resulting in an indifference to pain. This highlights that potentially there are differences dependent on modality and type of pain. In this case there could be a difference between acute pain experience and visceral pain (deep tissue pain). There could also be differences between autistic individuals. These accounts, however, have limited utility in establishing whether altered pain responses are generalisable to the wider ASD population. Frequently relied on cases may represent a variance in pain response that occurs in the population (Backonja et al., 2013; Maier et al., 2010; Rolke, Baron, et al., 2006) and therefore, may not be representative of pain in ASD.

Further to this, the nature of the environment itself, particularly a clinical observational environment, may have a role to play in pain response. Muskat et al., (2014) conducted qualitative interviews with parents and Health Care Professionals (HCPS) regarding experiences in hospitals in relation to autistic children. A recurring theme was that the hospital environment, alongside having ASD, presents itself with a range of challenges, namely pain and the consequences of this. For example, HCPS observed that autistic individuals struggle to communicate their pain. Additionally, they also observed that the procedures resulted in a lot of contact that autistic individuals appeared hypersensitive to. The lack of communication and the behavioural consequences result in a difficultly interpreting the nature, location, and intensity of their pain. Parents support these observations, with one observing, “he may not express pain the same way another patient would” (pp. 485 Muskat et al., 2014). In the example above, the researchers conclude that both observers perceived an alteration in pain in ASD. However, both these participant

groups are bringing separate subjective experiences and perspectives that are fundamentally different. This is similarly true for the professionals doing clinical observations whose training or experience or role is linked to a professional experience of ASD and atypicality. For example, the remit and focus of medical practitioners working with autistic patients is to alleviate symptoms and provide professional care. Relationships between the patients and these participants are also fundamentally different, one being personal and one being professional. In responding to the research questions, parents are likely to draw on their experience of their child, whereas health care practitioners are more likely to draw on a wider professional experience. A quantitative approach could be a more robust, consistent form of data gathering because the construct is more clearly defined, and therefore people are expected to answer in the same way. This results in being able to compare results between observers.

1.13 Observation of Pain in ASD During Medical Procedures

The aforementioned observational accounts of ASD have one commonality, they frequently describe autistic individuals and their pain experiences but there is little comparison to how individuals without ASD compare. Group comparisons are particularly important because they help to control for factors that may influence the relationship between ASD and pain. A number of studies have attempted to consider this limitation by observing both groups during medical procedures or in everyday settings, such as venepuncture or day care, whilst others have sought to compare observations across different observer types, or a mixture of these approaches. Importantly, these studies observe both facial expressions and behaviour in a more controlled experimental way than the aforementioned clinical observational work.

Using the Child Facial Coding System (CFCS); a system based on physiological anatomy of muscular movements and connections, Nader et al., (2004) and Rattaz et al., (2013), reported that autistic children had typical facial expressions to venepuncture, one that increased at needle insertion and decreased after removal to recovery. This was in comparison to those with Developmental Delay (DD) and those without ASD or DD, employing a more robust methodology than the aforementioned literature. Additionally, Messmer et al., (2008) had the videos from the Nader et al., (2004) study coded by undergraduate psychology students. Students were asked to read information about autistic children in which their experiences with pain were described and rate the observed pain using a VAS. This pain description was manipulated to either reflect that autistic children either appeared to feel pain more than other children, less than other children or that their experience was the same. Results indicated that manipulating information about pain did not impact on pain observation ratings, supporting those reported by Nader et al., (2004) and Rattaz et al., (2013), in that there were no differences reported in overall pain reactivity between the ASD group and controls. Nader et al., (2004), additionally reported that the ASD group showed greater facial activity only at needle insertion. In measuring facial expressions to routine immunisations in infants Mercer and Glenn, (2004) reported that the facial expressions were more complex. The Maximally Discriminative Facial Movement Coding System (MAX) system not only measures facial expressions from the upper, lower and eye/nose regions of the face, similarly to the CFCS, it additionally provides an opportunity for coding emotions in different areas, called blended expressions. Although there were similar reports of fewer painful expressions compared to controls, there were greater blended expressions. Therefore, it is possible that there is greater complexity of emotions being expressed during painful medical procedures.

Alongside facial expressions, both Nader et al., (2004) and Rattaz et al., (2013) measured wider behavioural expression of pain, using either an Observational Scale of Behavioural Distress or the Non-Communicating Child Pain Checklist (NCCPC). In comparison to controls, the ASD group showed a marked distress to venepuncture (Nader et al., 2004; Rattaz et al., 2013). This behavioural distress also continued for longer in the ASD group compared to controls (Rattaz et al., 2013). This delayed recovery supports the idea that painful medical procedures lead to distress in ASD, as highlighted by HCPS in their observations. One of the most concerning issues from the results of this study, is that in comparison to controls, only 46% of autistic individuals receive local anaesthetic compared to 67% of controls. However, why this was the case is unclear.

This finding of increased behavioural distress is however, not consistently reported. Tordjman et al., (2009) observed a decreased level of behavioural reactivity during venepuncture using the Pre-linguistic Behavioural Pain Reactivity Scale (PL-BPRS). For autistic individuals, compared to typically developing controls matched on sex, age and stage of puberty, there was an absence of pain behaviour, defined as an absence of reflexes rather than appearing to withstand pain. Of note is that observers witnessed very specific ASD responses not normally associated with pain that have yet to be considered in the wider literature. For example, an increase in aggressive behaviours, Self-Injurious Behaviour (SIB), and social withdrawal. This increased SIB could be occurring as a reaction to distress as a result of the procedure. Furthermore, autistic participants, although showing an indifferent pain response to the venepuncture, had robust physiological pain responses that matched the controls (Tordjman et al., 2009). There was elevated heart rate and plasma β-endorphin levels, demonstrating that although there was a decrease in behavioural expression, they may still have experienced pain. This is of particular importance, in that the expression may not fully represent the internal subjective experience or that there may be a specific ASD

pain response, which observers fail to consider because they are behaviours not typically associated with pain. Furthermore, social withdrawal, a response not typically observed in children when experiencing pain, may highlight the importance of considering the social characteristics that define ASD in relation to pain.

Additionally, Tordjman et al., (2009) asked caregivers in day care and parents at home to observe the autistic children prior to attending the clinic for venepuncture. Caregivers and parents were asked to report on overall daily pain reactivity. However, only mean values of the number of autistic children were reported. Interestingly, there was a greater number of autistic children reported as being hypo responsive, i.e., appearing to withstand pain at home by parents. For day care, the greater number of participants were reported as having normal responses to pain. This may point to important social contextual factors in the expression of pain, particularly in the differences between observing people in medical procedures compared to everyday experiences. Gilbert-MacLeod et al., (2000), used the Dalhousie Everyday Pain Scale and six observers to measure pain reactivity in 24 children with developmental delay (DD) and 36 without developmental delay in a day-care setting. Those in the DD group showed less intense distress responses and engaged in no response more often than other potential responses such as facial action, verbal comments, crying and screaming.

Those in the DD group also engaged in less help-seeking behaviour than those in the control group (Gilbert-MacLeod et al., 2000), suggesting that autistic individuals could be employing internalising behaviours more often than the typical help-seeking response, further supporting the notion of a behaviourally distinct pain response. Internalising behaviours, also known as passive pain behaviours, include but are not limited to, diverting attention, self-speak or reinterpreting pain (Buckelew et al., 1992; Lawson et al., 1990) and have been

shown to result in fewer observable pain behaviours (Buescher et al., 1991; Spinhoven et al., 2004). Importantly, children undergoing lumbar puncture were shown to engage in similar behaviours to the previous study's autistic individuals, including silence, lack of motion, sensory withdrawal or ignoring with lack of acknowledgement of pain or those around them (Broome et al., 1990). Passive pain behaviours (internalising) are not a determinant of pain ratings, such that those employing internalising versus active behaviours have similar pain ratings (Broome et al., 1990; Samwel et al., 2006), which may go some way in providing insights into why the research simultaneously reports autistic individuals as indifferent to pain, whilst there is pain ratings comparative or higher than controls. However, the degree to which autistic individuals may utilise these internalising behaviours is yet to be explored.

1.14 Parent/Self Report of Pain in ASD

Although parent report is still reliant on the pain expression and pain behaviour in the same way clinical observation is, the relationship is more intimate. Therefore, parents may be better at observing changes in behaviour and could be considered as having more insight due to having more contact and experience of the child (Sacrey et al., 2018; Schopler & Reichler, 1972). Some researchers have therefore asked parents to report on their child's pain experiences. The earliest of these studies showed parents reported that their autistic child was non-reactive to cold temperatures in comparison to a group with "mental retardation" and controls (Olof Dahlgren & Gillberg, 1989) who were reactive. However, other items that related to pain such as "he was exceptionally sensitive to pain" or, "he had unusual reactions to pain" (pp. 173) did not yield any differences. This theme of indifference continues with 22% of parents reporting low pain sensitivity and 21% reporting very low pain sensitivity in their autistic child (Militerni et al., 2000). A limitation of both these studies is that their approaches were to measure general symptomology of ASD and not pain specifically. Others

who have used more specific sensory measures such as the sensory profile have shown higher tactile sensitivity (Rogers et al., 2003) compared to those with Fragile X, those with DD and controls. This over-responsivity was also a significant predictor of abdominal pain in autistic children (Mazurek et al., 2014). Kern et al., (2006) further defined touch sensitivity as either sensory seeking or sensory defensiveness, showing that there could be subgroups of individuals experiencing very opposing reactivity to touch. Additionally, there was a decrease in dysfunction as age increased. Potentially, as individuals get older, they learn to negotiate the sensory world and may employ a range of tactics that help to modulate these extreme sensations. Of note is that when considering under-reactivity to pain, the 43% reported by Militerni et al., (2000) is supported by Klintwall et al., (2011) who reported under-reactivity to pain in 40% of their sample using structured interviews with parents, this was despite differing methodologies. Specifically, 22% reported under-reactivity to cold and 7% to heat. Over reactivity to touch was also reported in 19%. Interestingly language and cognitive level was not associated to sensory deficits, which has been previously suggested. Those who had toe-walking, meltdowns and sleep problems as symptoms had more affected sensory modalities, which points to pain response being related to very specific ASD symptomology.

Mandell et al., (2005) asked parents and caregivers about the quality and quantity of services and support they had received in terms of caring for their autistic child. Although this was regarding services, oversensitivity to pain was also reported in the sample and was associated with a 0.6-year increase in the age of diagnosis, suggesting that pain can mask the diagnosis of ASD. This could be because when a child presents to a clinician with pain, or pain related issues, that clinicians are looking for organic and not developmental causes. Only once pain is relieved or causes identified, or potentially that no organic cause can be determined, is there a wider consideration. Additionally, at the time a medical professional is

seeing a patient, they may be assessing both pre-pain and pain associated psychopathology. For many autistic individuals, chronic pain is comorbid (Clarke, 2015; Lipsker, Bölte, et al., 2018), and many of the co-morbid conditions associated with ASD have also been shown to follow pain, or are the result of painful conditions: anxiety, depression, sleep problems (Deliens et al., 2015; Hollocks et al., 2019; Rosen et al., 2018; Thompson et al., 2016). As such, it is difficult to make a distinction between psychological factors following pain, or pain caused by psychopathology (Fishbain, 2002), which may further delay the diagnosic procedure. Additionally, any medical interview should always start with a discussion with a patient (or carer) where the patient is encouraged to discuss which factors are most important to them. Pain is salient; therefore, it is likely that this could dominate or be prioritised in conversation, with psychopathology symptoms seeming less salient.

Diagnosis is also reliant on deductive-driven hypothesis testing ((Elstein & Schwartz, 2002; Moayyeri et al., 2011). This process is then subject to the skill of the clinician in deductive reasoning, but deductive reasoning can be a long process. It is possible that pain adds additional complexity when determining ASD diagnosis. Furthermore, research exploring delayed diagnosis in mental disorders associated with ASD, such as anxiety, also report an average of 5 (Ricky et al., 2017) to 9 years (Wang et al., 2005) years delay. This delay is greatest in those with activity limitations which included dexterity and pain, both of which have been reported in those with ASD, alongside anxiety (Bremer & Cairney, 2018; Buckelew et al., 1992; Rosen et al., 2018; Whyatt & Craig, 2013). Such complex cases are, therefore, likely to add further duration to the lengthy deductive reasoning process and delay diagnosis.

Alongside applying validated and reliable assessment tools that enable formal diagnosis, the DSM starts with cross-cutting symptom measures, which are used to rate

symptoms in a variety of domains which are not aligned with one diagnosis (APA, 2013). When causes of an illness or symptom is not certain, the ways of classifying the dysfunction in health are potentially less intuitive and require greater clinician investment, deduction, and hypothesis testing. Soft tissue pain is one such symptom. The reason this is important behaviourally, is because its absence made a patient a candidate for DSM diagnosis of pain disorders on the previous Axis I. However, if a patient was diagnosed with soft tissue pain disorders, they were then diagnosed with a pain disorder on axis III. Therefore, in context of pain, the presence of soft tissue pain could determine whether a person received a mental disorder diagnosis (APA, 2013; Fishbain, 2002). Since there is co-morbidity in ASD with soft tissue pain, then it is possible that this further impedes or delays diagnosis (Clarke, 2015; Lipsker, Bölte, et al., 2018), even under the new DSM structure that although does not involve the previous axes, still lists these as medical conditions, not psychiatric. This further highlights the need to understand pain in this population, specifically if it is likely to mask ASD at an early age and delay diagnosis. Delayed identification results in delayed engagement with services and so presents as a missed opportunity to aid the health and level of functioning of the individual (Berg et al., 2018; Fountain et al., 2011; Hertz-Picciotto & Delwiche, 2009).

Self-reporting of pain makes it possible to understand the subjective experience of autistic individuals. Some studies have looked at not only self-report but parent reports alongside this allowing us to compare the subjective with the observer. Using self-reported questionnaires Minshew and Hobson, (2008) found that autistic individuals had sensory sensitivities in the domains of tactile sensitivities, low pain/temperature thresholds and other sensitivities, supporting the earlier findings of the parent report studies. More individual differences in the ASD group were present. Seventeen of the 60 autistic participants had eight or more sensory sensitivities, which was in stark contrast to the control group where

none reported as many as eight sensory sensitivities. These sensitivities are also reported by the participant's parents. Supporting the notion that parents may be better placed to understand the experiences of their child. These findings were similarly reported by Tavassoli et al., (2014) using just the tactile aspect of the sensory profile.

Bandstra et al., (2012), however, found no difference when autistic children were compared to IQ–matched controls. Parents and autistic children reported how much pain they would expect if a particular event occurred given to them as a short vignette. Self-and parent-report showed that pain expectations were the same for both groups. There was no difference between what the parents reported versus the self-report. Although in this instance the methodology showed that there is adequate learning around painful experiences in so much that when looking at vignettes of painful experiences participants are able to give an expectation of whether that incident would be mildly moderately or extremely painful.

There are a number of limitations to such approaches. Mainly, they rely on accurate recall of the experience and the ability to introspect and compare one's own experience with that of others. These are not easily achieved abilities, particularly as they may be impaired in the ASD group due to the core feature of social deficits. This also requires parents to be able to infer not only their own child's pain, but also how it compares to other children's experiences. For this reason, results have to be considered with caution however, they do provide an important account of the perceived pain experiences that supports the autobiographical and case study accounts. Despite these limitations, self/parent report or clinical observation remains the most widely used methodology in the literature. Meaning that the evidence for any pain differences is largely based on the report of naturally occurring pain, rather than on experimental examination.

1.15 Psychophysical Pain in ASD

A psychophysical methodology tells us if a participant can detect and discriminate a noxious stimulus, as well as how much pain was felt and how unpleasant the sensation was (Moore et al., 2013; Zaccagnino & Nedeljkovic, 2017), thus, offering us a controlled and objective approach to the study of pain in ASD. Several studies have been conducted using this methodology, two of which have examined pain thresholds in ASD in the context of empathy (Bird et al., 2010; Fan et al., 2014). Bird et al., (2010) presented participants with electrical pain stimulation at 100 Hz, 4ms pulse length, 1 s duration and asked participants to rate on a 20-point Likert Scale (-10 pleasant to +10 unpleasant) how unpleasant the pain was. Although threshold data is reported the exact method for determining threshold is ambiguous. Findings reveal that autistic individuals did not significantly differ in their pain thresholds compared to sex and age matched controls, nor did their unpleasantness ratings, except for the low pain, where autistic individuals reported this as being unpleasant compared with controls who reported it as pleasant. Therefore, it appears that autistic individuals subjective experience was negative even when thresholds were the same. In contrast to these findings, Fan et al., (2014) examined pressure pain thresholds in adolescents and found that autistic individuals reported lower pain thresholds compared to healthy controls. Lower pain thresholds were correlated with more autistic traits. These studies are contradictory in their findings. There are, however, shared limitations to these as neither study was primarily interested in testing pain thresholds, the methods are therefore not standardised, nor comparable to each other. Additionally, the methods for determining thresholds in both studies are ambiguous, limiting contrasts further. However, it is interesting to note that lower pain thresholds were coupled with more self-reported autistic traits.

Psychophysical studies that directly measure electrocutaneous and vibratory thresholds, similarly, show a hyperresponsivity to electrical stimuli and vibratory stimuli

(Blakemore et al., 2006; Cascio et al., 2008; Yasuda et al., 2016). Not only did autistic individuals require less energy to detect electrical stimuli than controls, but they also report it as less discomforting, signifying that the affective qualities of the stimuli are different to the physical percept. Those studies using vibrotactile stimuli reported that adults diagnosed with Asperger's or ASD had lower tactile perceptual thresholds for 200Hz and 33Hz vibrotactile stimuli, implying a specific hypersensitivity in the Pacinian corpuscle's receptor pathway (the receptor which is responsible for detecting rapid vibrations on the skin; Blakemore et al., 2006; Cascio et al., 2008). Lower pressure thresholds were reported in autistic adults further supporting the notion of tactile hypersensitivity (Chen et al., 2009; Fan et al., 2014; Riquelme et al., 2016). In contrast, in a small sample of autistic children, there was no tactile perceptual threshold difference for vibrotactile detection (Güçlü et al., 2007), nor were there differences between autistic adults and controls for light touch (Cascio et al., 2008). There is a need for further exploration in this domain as touch is a proximal sense, with atypical responses reported with high frequency in the ASD population (Marco et al., 2011). In the anecdotal evidence, touch is described as an aversive experience, which links with the current definition of pain. Additionally, tactile thresholds represent a test of large fibre neuropathies, pressure pain investigates both cutaneous and deep pain, whilst dysfunction in the tactile domain should be tested with both static and dynamic stimuli. Furthermore, threshold deviations in the aforementioned stimuli, are found in those with painful conditions (Koltzenburg et al., 1992; Maier et al., 2010; Marchettini, 1993; Ochoa & Yarnitsky, 1993; Rolke, Baron, et al., 2006). By testing vibration, pressure and light touch, using both static and dynamic stimuli, Fründt et al., (2017) provides a systematic study to the tactile domain. Using a dynamic mechanical allodynia (DMA) test, wherein participants are stroked with a range of materials that are typically innocuous and reported that DMA was present in a

subgroup of individuals. This is of particular note because this does not occur in those without neuropathy or controls (Backonja et al., 2013; Rolke, Magerl, et al., 2006).

Hypersensitivity has additionally been reported in the thermal modality. Autistic individuals had reduced hot and cold pain thresholds compared to healthy controls; however, their detection of hot and cold temperatures was comparable to their healthy control matches (Cascio et al., 2008; Yasuda et al., 2016). In a sample of adolescents, the reverse was the case (Duerden et al., 2015). Autistic adolescents required a higher temperature for detecting a change towards warmer or cooler temperatures compared to healthy controls, however, their thermal pain thresholds were comparable. Additionally, using similar methods, Williams et al., (2019), also show no difference in thermal pain thresholds in adults. Interestingly, paradoxical heat sensations (where alternating cold and warm temperatures are applied, and a report of pain is given as individuals experience a painfully hot sensation rather than the cold that is occurring) have been reported in a subgroup of autistic individuals (Fründt et al., 2017).

Overall, the research is limited by the focus on one or a few modalities, rather than encompassing the entire system. Comparisons are difficult to draw because not only do samples differ, but so do the methodologies. Additionally, as in the case of the empathy studies mentioned above, pain sensitivity is a secondary outcome of interest rather than a primary outcome. Although Fründt et al., (2017) have conducted the most comprehensive battery, this battery still fails to measure central sensitization. The findings of both dynamic mechanical allodynia and paradoxical heat sensations in a subgroup of autistic individuals point to the need for a measure of central sensitization, as well as its absence from the psychophysical research all together.

1.16 Pain Research and Developmental Theories of ASD

Additionally, this research measures one component of pain – the periphery, without consideration of other potential cognitive or social aspects of pain. Changes in pain processing may be the result of changes at one or more sensory processing stages, ranging from the peripheral receptors in the skin, spinal synapses, the brain's perceptual system, descending control through to cognitive or social processes (Cascio et al., 2008; see secion 1.8 pain model). The cognitive processing of pain can be investigated to determine top-down effects. Other cognitive aspects such as pain motivation or attentional effects could be another avenue to be considered.

Many of these factors also have a role in current developmental theories of ASD. For example, The Social Orienting Hypothesis posits a disruption to the mechanism that prioritises attention to social content, resulting in a lack of comprehension and social learning which reinforces the attentional differences. The Social Orienting Theory places emphasis on reward value, wherein a reduction or absence of the rewarding nature of a stimulus results in reduced engagement, which reinforces the limited reward value (Unruh et al., 2016). Take for example, a child who is indifferent to pain, the Social Orienting Hypothesis could suggest that they missed out on learning to communicate their pain because of their different attentional focus at critical developmental periods.

In contrast the Social Motivation Theory suggests that this indifference may reflect a lack of motivation to engage with the learning process or may even suggest that motivation to engage in the stimulus itself is less or different (Chevallier et al., 2012). Pain behaviours can be positively reinforced by a parent or carer showing attention. In particular, pain reducing or pain promoting parental behaviour significantly impacted perceptions of pain (Chambers et al., 2002) and children of chronic pain patients chose more pain related responses to

scenarios and were more external in their health locus of control than control children (Rickard, 1988). Highlighting the interaction between associative learning and pain communication, indeed on pain experience itself too. However, each of these theories are in decline as neither account for the uneven profile in abilities across the ASD spectrum (Johnson, 2014), nor do we fully understand pain associative learning in ASD.

Non-social domain theories could suggest that the ability to switch attention to the pain stimulus is poorer in ASD (Gliga et al., 2014). Whilst theories adopting a developmental trajectory perspective, posit that subtle differences in the relationship with the environment in early childhood place autistic individuals on a particular trajectory resulting in larger differences at the age when diagnosis becomes possible (Flectcher-Watson & Happe, 2019; Karmiloff-Smith, 2006). One such difference may be the resulting DSM criteria of indifference to pain, although research establishing this link is required. However, there is likely a connection in that biological substrates serving pain, emotion, cognition, language and behavioural competence, also follow developmental trajectories (Backonja et al., 2013; Brewer et al., 2020; Hatfield, 2014; Levy et al., 2018; Maier et al., 2010; Simons & Tibboel, 2006). Much like these theories of ASD, it is likely that attentional and reward differences act reciprocally.

Some research has examined how atypical sensory processing impacts upon theoretical accounts of ASD, in particular those theories which propose problems with higher order perceptual integration. Leekam et al., (2007) reported that few individuals had sensory abnormalities solely in one modality, or domain as measured by the sensory profile. They propose that the problem lies within sensory integration and that this difficulty is connected to social communication difficulties. Social functioning in typical populations who experience pain is impacted, therefore it is reasonable to assume this could be similar if not

exacerbated in ASD considering the existing difficulties. Foss-Feig et al., (2012) report that for the tactile modality, sensory hypo-responsiveness correlates strongly with increased social and communication impairments, suggesting a link to social dysfunction. However, Rogers et al., (2003) did not find any associations between scores on the short sensory profile and the social and communication subscales of the Autism Diagnostic Interview-Revised (ADI-R). The problem with this is that it is self-report measures only, correlated subscales are not reflective of causal relationships and it would be incorrect to infer so (Vaughan, Failla, et al., 2019).

1.17 Aims

Evidence to date of altered pain processing in ASD is largely reliant on case evidence and observations which has yielded contradictory findings and suffers with methodological flaws. Namely, it relies on one person's experience to represent a whole group, or an observer's judgement that is subject to bias. These studies are thought however, to have ecological validity because they include all the factors of a naturally occurring context (Shamay-Tsoory & Mendelsohn, 2019). However, lab-based studies offer an objective methodology, that allows for the control of extraneous variables (Henshel, 1980). Experimental evidence has focussed on the periphery using a psychophysical approach. However, this is generally limited to thermal and tactile modalities, with mixed findings (Blakemore et al., 2006; Cascio et al., 2008; Güçlü et al., 2007). To date, there has been no research that considers the cognitive aspects of pain in ASD, in particular, motivation, or pain-related fear, except to include clinical level depression and anxiety as participant descriptors or to use these as exclusion criteria. The social communication of pain in ASD, has been largely reliant on observational studies, with little control of extraneous variables. The following studies, therefore, aim to consider a wider range of modalities in the

psychophysical approach, the cognitive and the social communication of pain, in order to experimentally investigate pain in ASD. In order to address these gaps, the aims of this thesis are as follows:

1. Chapter two will examine whether the absence or insensitivity to pain described in the anecdotal evidence is the result of changes in the peripheral processing of a stimulus evoked response. Participants will be tested using a comprehensive psychophysical test battery that will test all modalities, including detection and pain thresholds. As this battery incorporates subjective reports as well as measures of threshold and tolerance, its strength lies in the relationship between physical stimuli and their subjective correlates or percept's.
2. Cognitive factors, including attention, motivation and expectations influence the experience of pain (Eccleston & Crombez, 1999; Moore et al., 2012; Van Damme et al., 2010), though there has been little consideration of these factors in the ASD experimental pain literature. The aim of Chapter 3 is to determine if the atypical pain behaviours observed in the anecdotal evidence are the result of a greater reduction of pain behaviours by other salient stimuli. It aims to explore whether a nociceptive stimulus evokes an emotional state to avoid it, and if salient stimuli attenuate avoidance behaviour.
3. Social deficits are a core feature of ASD (APA, 2013), whilst pain is subject to social influences and is communicated to the external environment, where these behaviours can hold social value and meaning. Effective communication relies on the interpretation of these behaviours, both verbal and body language, by an observer. However, the observational work is largely biased and utilises a range of methods which are not inherently objective as they still rely on a judgement of the affective state of an individual. Therefore, Chapter 4 aims to explore whether the subjective

experience is communicated in ways that may result in the described insensitivity, or absence of pain, or if there is a set of ASD specific pain behaviours that have so far not been considered but have been observed (Tomchek & Dunn, 2007).

Chapter 2. Psychophysical Approach to Pain in Autism Spectrum Disorder

Chapter two is comprised of two experiments, taking a peripheral and psychophysical approach to the study of pain in ASD, both clinical ASD and ASD traits. Experiment 1 is comprised of unpublished data and is presented below in chapter 2A. The introduction presented in this Chapter, alongside the methods outlined in section 2A.2 and rationale for Experiment 2 and Experiment 2 itself (see Chapter 2B) have been published in The Journal of Autism and Developmental Disorders (see Appendix A) and is presented in line with the Author Archiving and Re-Use guidelines, namely that it is verbatim to the published work.

Vaughan, S., McGlone, F., Poole, H., & Moore, D. (2019). A Quantitative Sensory Testing Approach to Pain in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders.* Doi: 10.1007/s10803-019-03918-0.

Chapter 2. General Introduction

In addition to the most striking lifelong effects of impaired communication, socialization and restrictive/repetitive behaviours in ASD, there is a high prevalence of sensory perceptual anomalies (Baranek, 2002). Evidence for which has relied on autobiographical, observational or behavioural measures (Moore, 2015) which has demonstrated, amongst an array of sensory disturbances, an absence of typical pain behaviours (e.g., absence of hand withdrawal reflex or a lack of protective body positioning) when encountering pain (Bursch et al., 2004; Gillberg & Coleman, 2000; Mahler et al., 2018; Rothenberg, n.d.). There is further evidence that autistic individuals have aversions to touch (Grandin, 1992, 1995; Williams, 1999), signifying that light tactile sensation might be a source of discomfort, indicating a potential hypersensitivity to tactile stimuli (Kaiser et al., 2016; Moore, 2015). However, such methods are typically not generalizable because it is unclear whether the case investigated is representative of the wider body of "similar" instances. Further validation of this phenomenon is given by the re-incorporation of sensory responses as a feature in diagnostic texts suggesting that it is a central clinical finding in autism (APA, 2013). There is, however, a dearth of rigorous psychophysical experimental evidence to support these claims. Therefore, the current Chapter aims to clarify the characteristics of *pain* sensitivity associated with ASD using a psychophysically robust experimental case-control design.

Pain is multifaceted, defined as a distressing experience associated with actual or potential tissue damage; with sensory, emotional, cognitive and social components (International Assosiation for the Study of Pain, 2020; Williams & Craig, 2016). Together, the percept, and the subjective reaction act as a warning system so that individuals learn to avoid dangerous stimuli (Yasuda et al., 2016) whilst also promoting behavioural analgesia

(Eccleston & Crombez, 1999). A disruption to this system could result in a lack of these learned behaviours.

Potentially nociceptive (painful) stimuli are detected by specific somatosensory receptor neurons (nerve fibres), known as nociceptors which can be classified into three different types: Aβ, Aδ and C-fibre (Besson, 1999; Delmas et al., 2011; Djouhri & Lawson, 2004; Lumpkin & Caterina, 2007). Nociceptive messages are typically mediated by Aδ, and C-fibres, the functionality of which, in neurotypical populations, has been well described (for reviews see Basbaum & Jessell, (2000); Basbaum et al., (2009); McGlone & Reilly, (2010); Meyer et al., (2006). Before these signals generate a perception of 'pain' they are centrally integrated in the dorsal horn of the spinal cord and transmitted to the brain via the spinothalamic tract (Basbaum & Jessell, 2000; Iggo, 1977; Nafe, 2007; Schiller, 1956). This internal pain experience is then communicated which can be observed in stereotyped pain behaviours (Craig, 2015) and self-report – and which is neither simply, nor directly, associated with the level of nociceptor activity; nociceptor activity can produce more or less pain depending on a range of factors (John D. Loeser, 2012). De-coding whether these underlying mechanisms are altered in autistic individuals will give insight into the pain behaviours observed in this population.

Recently a few studies have begun to disentangle the underlying sensory mechanisms of somatosensory dysfunctions in ASD using psychophysical methods, the earliest of which focused on tactile sensitivity, investigating this with vibrotactile stimuli (Blakemore et al., 2006; Cascio et al., 2008; Güçlü et al., 2007). Blakemore et al., (2006) reported a frequency dependent hypersensitivity in adults with Asperger's compared to neurotypical controls. Conversely, Güçlü et al., (2007) and Cascio et al., (2008) report no significant difference

between the vibrotactile thresholds of children and adults with ASD and controls, therefore effects may be a result of specific frequencies, sites or other methodological differences.

Regarding pain perception, the focus has generally been towards thermal testing, with similarly mixed findings. Thermal pain hypersensitivity but normal thermal detection has been reported in adults with ASD (Cascio et al., 2008). Adolescents are reported to have the inverse results; normal thermal pain thresholds, but a hyposensitivity to innocuous thermal stimuli (Duerden et al., 2015). No differences in thermal detection thresholds and electrical pain were observed by Yasuda et al., (2016) and Bird et al., (2010), however, pressure pain thresholds were lower in autistic individuals compared to controls (Fan et al., 2014). This pattern of findings indicates no systematic change in psychophysically determined pain thresholds for autistic individuals compared to controls. This is not to imply that pain response in ASD is typical, both Fründt et al., (2017) and Duerden et al., (2015) report paradoxical heat sensations, a phenomenon where gentle cooling is perceived as hot or burning (Magerl & Klein, 2006), in several of their autistic participants. This phenomenon usually does not occur in healthy individuals. Considering the paucity of evidence paired with the mixed results, probably due to the heterogeneity of participants (e.g., ASD symptom severity or comorbidities) and differences regarding methods and sub-modalities investigated, the disentanglement of the underlying mechanisms of somatosensory dysfunctions in ASD is limited and there is no gold standard on how these features should be assessed in ASD.

Several recent investigations (Blakemore et al., 2006; Cascio et al., 2008; Duerden et al., 2015) have utilised methodologies that have been collated into the standardised Quantitative Sensory Testing battery developed by The German Research Network on Neuropathic Pain (DFNS; Rolke, Magerl, et al., (2006)). This method allows for the quantification of clinically significant perception and pain thresholds (Werner et al., 2013)

assessing the function of small and large diameter nerve fibres (Hansson et al., 2007). If used in its entirety this method allows researchers to assess nerve function across the full range of modalities; vibration, pressure, thermal, and mechanical (Moloney et al., 2012) in a standardised manner. The focus on a single or a limited number of these sub-modalities limits previous studies. One study, however, has utilised this full battery, therefore, providing the most comprehensive assessment of somatosensory function in ASD to date (Fründt et al., 2017). More extreme somatosensory responses (i.e., hyper- or hyposensitivity) or somatosensory phenomena not typically observed in those without neuropathy (i.e., dynamic mechanical allodynia or paradoxical heat sensations) were observed in the ASD group, however, there were no group differences reported for global or systemic changes in somatosensory function.

Chapter 2A. A Quantitative Sensory Testing Approach to Pain in Broader Autism Phenotype

Experiment 1 presented below is comprised of unpublished data.

Chapter 2A. Experiment

2A.1.2 Rationale

Research has shown that the broader autism phenotype (BAP), a subclinical presentation thought to be a milder manifestation of traits characteristic of clinically diagnosed ASD (Rutter, 2000; Sucksmith et al., 2011), is not only present in families where a child has been diagnosed with ASD, but also in typically developing households (Pisula & Ziegart-Sadowska, 2015; Wheelwright et al., 2010). In studies where clinical ASD sample sizes are small and a prevailing limitation (Blakemore et al., 2006; Cascio et al., 2008; Duerden et al., 2015), the BAP can allow for investigation using comprehensive experimental protocols which could be onerous to those with clinical ASD, whilst recruiting larger sample sizes. All of which enables the precise delineation between ASD related features and specific cognitive processes (Landry & Chouinard, 2016) without burdening an already vulnerable population.

More specifically, the BAP has been associated with sensory sensitivity (Robertson & Simmons, 2013). In one study by Voos et al (2013), neurotypicals with high autistic traits have greater aversions to touch, supporting some of the anecdotal research that reports similar experiences in autistic individuals. More recently, Mayer et al. (2017) investigated the relationship between sensory processing and autistic traits in 580 participants, 42 of which had high functioning ASD. Results revealed a significant relationship between subscales on the Sensory Profile and autistic traits, where there was a clear progression of sensory atypicalities in line with an increase in autistic traits. Participants were split into groups based on autistic traits rather than diagnosis, and after controlling for age, gender, and IQ (factors linked elsewhere to atypical pain response in ASD), sensory processing abnormalities were reported as being greater in the high AQ trait group compared to low AQ group and a

neurotypical group. Highlighting that the BAP and its associated behaviours exist out with ASD and therefore it is a useful foundation for work in sensory studies (Landry & Chouinard, 2016). However, except for Voos et al (2013), these studies have only used sensory questionnaires, that span a range of sensory signs and symptoms. Voos et al (2013), although using a psychophysical approach, have looked at affective touch. Therefore, even within the BAP there is a need to apply psychophysical methods that cover pain and touch across a range of modalities. Furthermore, since the BAP has been associated with sensory sensitivity (Robertson & Simmons, 2013), it is a useful foundation for work in sensory studies (Landry & Chouinard, 2016).

The standardised Quantitative Sensory Testing (QST) battery developed by The DFNS (Rolke, Baron, et al., 2006) is one such comprehensive protocol, typically used for assessing pain in typical populations, or indeed in clinical settings as a diagnostic tool for neuropathy (Backonja et al., 2013; Rolke, Magerl, et al., 2006). The full battery presents some challenges when applyied to autistic individuals. Autistic individuals can be highly anxious, with a high comorbidity to anxiety disorders (for review see Hollocks et al., 2019). This may mean that novel stimuli that are presented during QST tests may cause marked distress to these individuals (Spratt et al., 2012). Which in turn may influence responses, for example, they may respond earlier for fear of pain or intensity ratings may be higher due to fear of pain (for review see Kroska, (2016)). Additionally, autistic individuals frequently have communication difficulties and very specific communication needs (Baron-Cohen et al., 1997). In a protocol that requires very precise understanding of instructions and the ability to communicate at which point a stimulus is detected or becomes painful, such communication difficulties may lead to response errors. Therefore, testing the utility of this battery in a non-clinical but quantitatively similar population is a useful strategy.

The aim of this experiment is to determine a full QST profile and the utility of this in ASD prior to the recruitment of a clinical sample. Furthermore, this battery was extended to include a measure of pain tolerance utilising the cold pressor test (von Baeyer et al., 2005). Including tolerance allows a wider range of psychophysics to be measured; threshold (the minimum intensity of a stimulus that is perceived as painful), suprathreshold (increases the frequency of nociceptive messages) to tolerance (the maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation (Chapman et al., 1985; *IASP Terminology - IASP*, 2017). Tolerance also includes additional components such as pain motivation; to quantify said motivation; self-reported desires to avoid pain were measured. Lastly, electrocutaneous stimulation has been reported in ASD populations and therefore its inclusion allows for a comparison of findings (Bird et al., 2010; Yasuda et al., 2016)

2A.2 Methods

2A.2.1 Participants

Fifty-two healthy adults (31 males) without a diagnosis of ASD, covering an age range between 18 and 74 years were recruited (M = 27.98, SD = 13.73) and were screened for inclusion using an online health questionnaire. Participants suffering from chronic pain, a heart abnormality, eczema, epilepsy, or asthma were excluded. Additionally, they were asked specifically about any history of a psychiatric disorder or a diagnosis of a learning disability and were excluded if present. All participants were without pain medication or alcohol at least 24 hours before the investigation.

Participants were split into four equal groups (n = 13 per group), based on the number of autistic traits, measured by the Autism Quotient (AQ). Total scores were used to split the sample into quartiles representing the following groups: ‘low AQ’ (<11.75), ‘average AQ’

(<17.50), ‘above average AQ’ (<25.25) and ‘high AQ’ (>25.25). AQ quartile groups did not significantly differ on age $F(3,48) = .621$, $p = .605$ or other known covariates that affect pain responses, such as pain catastrophizing $F(3,48) = .310$, $p = .818$ (Pain catastrophizing scale [PCS]; Sullivan et al., 1995), pain anxiety $F(3,48) = 1.395$, $p = .256$ (Pain anxiety symptoms scale [PASS]; McCracken et al., 1992) or anxiety sensitivity $F(3,48) = .614$, $p = .609$ (Anxiety sensitivity index-3 [ASI]; Peterson & Heilbronner, 1987). There was significant group difference for gender $\chi^2(3) = 14.937$, $p = .002$, the distribution of males and females differed in each of the groups; see table 1 for descriptive statistics

Table 1:

Characteristics and questionnaire results of AQ groups

Characteristic	High AQ	Above average AQ	Average AQ	Low AQ	Total
No. of Participants	13	13	13	13	52
Gender Female	2*	2*	7*	10*	21
Male	11	11	6	3	31
Age	23.77 (6.43)	30.38 (16.87)	27.77 (14.55)	30.00 (15.30)	27.98 (13.37)
Autism Quotient (AQ)	30.69 (5.38)	21.15 (2.38)	14.31 (1.93)	9.77 (1.01)	18.98 (8.52)
Pain Catastrophizing (PCS)	19.54 (7.42)	19.92 (6.85)	16.62 (10.15)	17.23 (9.61)	17.58 (8.45)
Pain Anxiety (PASS)	39.49 (17.52)	30.62 (12.23)	31.69 (23.78)	25.69 (13.71)	31.87 (17.59)
Anxiety Sensitivity (ASI)	27.77 (16.97)	27.08 (11.26)	22.08 (14.19)	22.62 (11.03)	24.88 (13.43)

Note. All values are given as mean (*SD*). *p<.05. AQ (Autism Quotient)

The experiment was approved by Liverpool John Moores Ethics Committee (REC ref: 15/NSP/013) and all participants gave written informed consent.

2A.2.2 Materials

2A.2.2.1 Questionnaires

2A.2.2.1.1 Autism Quotient

Consisting of 50 forced choice statements, the AQ measures autistic trait severity, including clinically relevant traits using a 4-point likert scale from 1 (definitely agree) to 4 (definitely disagree). The subject scores one point for each question which is answered "autistically" either slightly or definitely agree. The questions cover five different domains associated with the autism spectrum: social skills; communication skills; imagination; attention to detail; and attention switching/tolerance of change. The maximum score is 50.

2A.2.2.1.2 Pain Catastrophizing Scale

The PCS is an instrument used as a measure of catastrophic thinking about pain consisting of 13 questions, using a 5-point Likert scale from 0 (not all the time) to 4 (all of the time). Participants were asked to reflect on past painful experiences and indicate to which degree they experience each of the 13 thoughts or feelings when experiencing pain. The PCS yields a total score (52) and three subscale scores assessing rumination, magnification, and helplessness. Several studies have supported the reliability and the validity of the PCS as a measure of pain-related catastrophic thinking (Meyer et al., 2008; Osman et al., 1997; Sullivan et al., 1995).

2A.2.2.1.3 Pain Anxiety Symptoms Scale

Pain Anxiety Symptoms Scale, consisting of 20 items (total score of 100), measures pain-related anxiety. Describing pain via fearful thoughts and rumination, physiological fear symptoms and avoidance of activities related to pain. Assessing these through 3 modalities; cognitive, physiologic and motoric, each item is scored form 'never (0)' to 'always (5) on how often an individual engages in each of the thoughts or activities described. PASS has been shown to be a reliable and valid measure of pain-related anxiety (Burns et al., 2000; McCracken et al., 1992).

2A.2.2.1.4 Anxiety Sensitivity Index

ASI measures the construct of anxiety sensitivity, across 18-items; the dispositional tendency to fear the somatic and cognitive symptoms of anxiety due to a belief that these symptoms may be dangerous or harmful. Each item is rated from very little (0) to very much (4) and yields a total score of 72. The ASI has been shown to be a reliable and valid measure of anxiety sensitivity (Kemper et al., 2012; Peterson & Heilbronner, 1987).

2A.2.2.2 Quantitative Sensory Testing

2A.2.2.2.1 Thermal detection and pain thresholds and the number of paradoxical heat sensations

Cold and warm detection thresholds were measured first (CDT, WDT), followed by thermal sensory limen (TSL), a procedure of alternating warm and cold stimuli, during which a measure of paradoxical heat sensations (PHS) was established; a phenomenon where gentle cooling is perceived as hot or burning (Magerl & Klein, 2006). Cold and heat pain thresholds were then determined (CPT, HPT). These tests measure Aδ (A-delta) and C-fibre mediated warmth, heat and cold sensations.

Baseline temperature of the thermode (9cm2 contact area) was set to 32°C, with cut off of 50°C and -10°C. All thermal tests were performed using a Medoc Pathway Advanced Thermal Stimulator (ATS). All thresholds were obtained with ramped stimuli (1°C/s) that terminated when the subject pressed a button. For thermal detection thresholds the ramp back to baseline was 1°C/s, while pain thresholds returned to baseline at the maximum device capacity of 5°C/s.

The final threshold for CDT and WDT was a mean value of three difference scores from baseline (for example, [WDT1-32+WDT2-32+WDT3-32]/3). The final threshold for TSL, was a mean of the difference value between the three pairs of temperatures i.e. (TSL1 - TSL2) + (TSL3-TSL4) + (TSL5-TSL6)/3. Both cold and warm pain was a mean value of the three threshold values (for example, [HPT1+HPT2+HPT3]/3). In addition to the TSL, participants were asked about paradoxical heat sensations the number expressed was recorded; that is whether the temperature was felt as cold, warm, hot or burning.

2A.2.2.2.2 Mechanical Detection Threshold

A standardised set of modified von Frey hairs (Opti-hair set, MARSTOCKnervtest) was used to measure mechanical detection threshold (MDT) i.e., touch sensibility mediated by Aβ fibres; by applying hairs to a uniform area of skin with a 1-2s contact time. Each hair has a small epoxy bead on a rounded tip in order to avoid nociceptor activation and exerts forces upon bending, between 0.25 and 512mN, graded by a factor of 2. Using “the method of limits”, five threshold determinations were made, each with a series of ascending and descending stimulus intensities. The final threshold was the geometric mean of these series.

2A.2.2.2.3 Mechanical Pain Threshold

Seven weighted mechanical pinprick stimulators (MRC systems) with fixed stimulus intensities that exert forces of 8, 16, 32, 64, 128, 256 and 512mN were applied to a contact area, with a 2s contact time, in order to measure mechanical (pinprick) sensory functions. Using "the method of limits"; stimulators were applied in an ascending order until the first percept of sharpness was reached, followed by a descending order until the first blunt percept was reached, five threshold determinations were made, each with a series of ascending and descending stimulus intensities. The final threshold was the geometric mean of these series.

2A.2.2.2.4 Stimulus/response Functions: Mechanical Pain Sensitivity (MPS) for Pinprick Stimuli and Dynamic Mechanical Allodynia

To obtain a stimulus-response function for pin prick evoked pain (MPS), the same seven set of pinprick stimulators were used (the heaviest pinprick force was about eight times the mean mechanical pain threshold). Participants were asked to give a pain rating for each stimulus on a 0-100 numerical rating scale: 0 indicating no pain, 100 indicating the most intense pain imaginable. This test detects pin prick hyperalgesia, a dysfunction of Aβ fibres. Inserted in between the pinprick stimuli, in order to obtain a measure of dynamic mechanical allodynia (DMA; a triggering of a pain response from stimuli which do not normally provoke pain, representing an increased response of neurons), a set of three light tactile stimulators of moving innocuous stimuli; cotton wisp exerting a force of 3mN, a q-tip exerting a force of 100mN and a standardized brush exerting a force of 200-400mN (Somedic, Sweden) were applied, each with a single stroke, 2cm in length.

A total of 50 stimuli; 15 tactile and 35 pinpricks, were delivered with the participant giving numerical ratings for each stimulus. These stimuli were presented in runs of 10,

pseudo random sequences, each consisting of three tactile and seven pinprick stimuli, each with a 10s interval (below the critical frequency for wind-up).

MPS was calculated as the geometric mean of all numerical ratings for pinprick stimuli, while DMA was the geometric mean of all rating for all three of the light touch stimulators.

2A.2.2.2.5 Wind-up Ratio

To establish a measure of wind-up ratio, a test of temporal summation (WUR; a frequency dependent increase in excitability of spinal cord neurons), the perceived intensity of a single 256mN pinprick stimulus was compared with that of a series of 10 repetitive stimuli of the same physical pinprick intensity (256mN, 1/s applied within an area of $1cm^2$). Participants gave a numerical pain rating representing the single stimulus, and then an estimated mean over the whole series of 10, using a 0-100 numerical rating, as described above. The whole procedure was then repeated five times. The wind-up ratio was calculated as the ratio of the mean of the five series divided by the mean of the five single stimuli.

2A.2.2.2.6 Vibration Detection Threshold

Vibration detection threshold (VDT) was performed with a tuning fork (64Hz, 8/8 scale) placed over the bony premise of the wrist (processus styloideus ulnae). VDT was determined with three series of descending stimulus intensities; measured by the number on a scale of 8, at which the stimulus ceased to be felt (8 meaning no vibration stimuli = 0Hz). The threshold is then the mean of three stimulus repetitions and evaluates vibration sensation mediated by Aβ fibres.

2A.2.2.2.7 Pressure Pain Threshold

The pressure pain threshold (PPT) was performed over the thenar eminence (muscle on the palm of hand at the base of the thumb) with a handheld pressure algometer (Somedic) with a $1cm^2$ probe area. This can exert forces up to 2000kPa. The threshold was determined with three ascending stimulus intensities, each applied as a slowly increasing ramp of 50kPa/s, until participants report a painful sensation. This evaluates pressure pain sensation mediated by Aδ and C-fibres.

2A.2.2.3 Additional Tests

2A.2.2.3.1 Electrical Pain

Electrical pain was performed on the ventral side of the forearm, over the median nerve, using a high voltage (HV) current stimulator (DS7A, Digitimer), which allows currents up to 1A with a maximum pulse duration of 200μs. Participants received stimuli in an ascending order (1mA) until the first percept of pain was reached, followed by a descending order (1mA) until the first non-painful electrical percept was reached. The final threshold was determined as the geometric mean of three series of ascending and descending stimuli. Additionally, the data was logarithmically transformed.

2A.2.2.3.2 Cold Pressor Test

A custom built cold pressor (Dancer Design), which maintains water in a stimulus tank at a predefined temperature (2°C) was used to measure cold pain threshold and tolerance. A control unit containing a temperature controller drives water taken from a reservoir of ice-water (maintained at 0°C) through the stimulus tank at a controlled rate. Water extracted from the stimulus tank is returned to the reservoir tank to be cooled by the ice. In the control unit two control mechanisms operate in parallel. The first is governed by

the temperature controller, which activates the drain pump to extract water from the tank at a rate determined by the difference between the actual water temperature (as measured by the thermistor) and the requested water temperature; 2°C in this instance, therefore maintaining the requested temperature to within 0.10°C. The second mechanism is governed by the PLC, which maintains the water level in the stimulus tank by activating the fill pump and valve at a rate determined by the level of the water in the tank (as measured by the water level sensor).

Pain threshold is defined as the elapsed time between arm immersion and the first report of a pain sensation. Pain tolerance is defined as the elapsed time until voluntary withdrawal of the hand. Since the Cold pressor test induces pronounced sympathetic activation and vasoconstriction, the maximum duration of limb immersion was set at 3 minutes.

2A.2.2.3.3 Avoidance Scores for Pinprick Stimuli including Stimulus/response Function (MPS/DMA)

To gain a measure of avoidance for MPA, DMA and WUR stimuli, participants were asked to rate how much they would like to avoid feeling any stimulus that was given a pain rating (a value above 0). This would provide an explicit measure of the subjective experience of the individual that extends beyond the implicit experience of the stimuli. Avoidance was rated using the same scale as the aforementioned QST parameters of 0 to 100; 100 being "would never like to experience the stimulus again". MPS avoidance was calculated as the geometric mean of all numerical avoidance ratings for pinprick stimuli, while DMA avoidance was the geometric mean of all avoidance ratings corresponding to the static stimuli. The wind-up ratio avoidance was calculated as the ratio of the mean of the five series avoidance ratings divided by the mean of the five single stimuli avoidance ratings.

2A.2.3 Procedure and Design

Each participant firstly answered the Autism-Spectrum Quotient (AQ; (Baron-Cohen et al., 2001). This was followed by the PCS, PASS and the ASI; known constructs to affect pain responses. Then participants underwent the QST battery developed by The DFNS (Rolke, Baron, et al., 2006). This standardized battery provides a sensory profile that consists of 13 parameters grouped into the following categories:

- Thermal detection and pain thresholds and the number of paradoxical heat sensations
- Mechanical detection threshold
- Mechanical pain threshold
- Stimulus/response-functions: mechanical pain sensitivity for pinprick stimuli and dynamic mechanical allodynia
- Wind-up ratio representing the perceptual correlate of temporal pain summation
- Vibration detection threshold
- Pressure pain threshold

These tests were always performed in the same order outlined in section 2A.2.2.2 and as recommended by The DFNS (Rolke, Baron, et al., 2006). Each participant received the same standardised set of instructions for each test, as described by The DFNS investigator brochure (see Appendix C for instructions). All tests were carried out on the dorsum of the right hand, with the exception of vibration and pressure pain (discussed in section 2A.2.2.2.6 and 2A.2.2.2.7).

Three further measures were used: electrical pain, two-point discrimination and a cold pressor test. Similar standardised instructions were developed based on DFNS instructions and given to each participant (see Appendix C). Tests were also performed in the order outlined in section 2A.2.2.3.

2A.2.4 Data Evaluation

In order to assess differences in sensory tests across different levels of AQ traits that mirrored the structure of the AQ questionnaire. In terms of a low AQ, an average AQ, above average AQ and high AQ traits group. Participants were split into quantiles using the scores from the AQ. This also facilitated addressing the impact of unequal group sizes impacting on findings via unequal variances between samples, particularly as ANOVA was being utilised for analysis.

For pinprick (MPS) and light touch (DMA), as well as their corresponding avoidance measures, a small constant (+0.1) was added prior to log-transformation to avoid a loss of zero-rating values (Bartlett, 1947; Magerl et al., 1998). All data except PHS, CPT, HPT, and VDT were logarithmically transformed. To compare a patient's QST data profile with control data, independent of the different units of measurement, patient data were z-transformed by subtracting the mean value of the corresponding published QST reference value followed by a division by the respective standard deviation; for each QST parameter using the following expression:

$$Z\text{-score} = (X_{\text{single participant}} - \text{Mean}_{\text{norms}})/SD_{\text{norms}};$$

This procedure meant that not only were known effects of gender, age and site controlled for, but also that we could compare our participants to The DFNS reference data. Additionally, it results in a QST profile where all parameters are presented as standard normal distributions. For clarity and ease, in order to think in terms of gain or loss of function, the algebraic sign of *Z*-score values was adjusted so that it would reflect a participant's sensitivity to this parameter. *Z*-values above "0" indicate a gain of function, when the patient is more sensitive to the tested stimuli, while a scores below "0" indicate a loss of function referring to a lower sensitivity. Thus CDT, WDT, TSL, HPT, MDT, MPT,

VDT and PPT required reversing, whereas CPT, MPS, DMA and WUR did not. For PHS and DMA it is a priori impossible to assess a pathological reduction, since these signs are normally absent in a healthy population. If the resulting *Z*-score exceeds 1.96, it is outside the 95% confidence interval of the standard normal distribution with zero mean and unit variance, independent of the original units of measurement.

All statistical calculations were performed with SPSS. Differences between groups were compared using multivariate analysis of variance (MANOVA), followed with post-hoc protected ANOVAs for all QST parameters. QST data were retransformed, and raw values are presented as mean ± SD to ease understanding. Where values are presented as *Z*-scores figures and tables' state as such. Group differences for the additional sensory tests were compared using analysis of variance (ANOVA), followed with post hoc pairwise comparisons; values for these are presented as mean ± SD.

2A.3 Results

It was possible to obtain all QST data in 51 of 52 participants; a technical issue resulted in the loss of one individual's thermal parameters. In three cases WUR, and in six cases WUR avoidance scores, could not be calculated because the denominator (mean rating for the single stimulus) was zero. One participant's wind-up ratio could not be calculated because despite using the predefined pin prick (256mN) no feeling of pain was reported (score of zero for all stimuli), as well as no desire for avoiding the stimulus (score of zero). An additional 6 individuals also reported no avoidance scores for WUR.

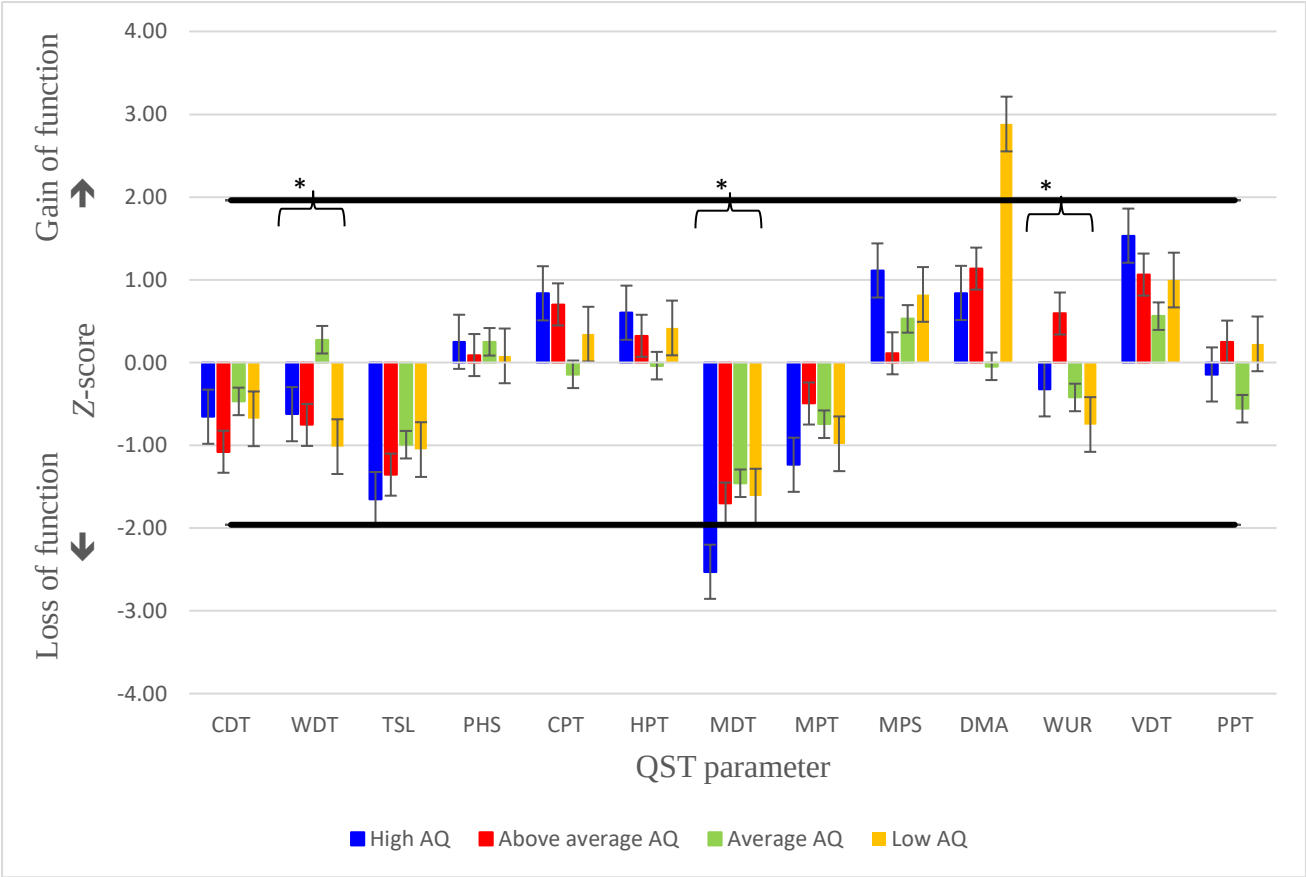
2A.3.1 QST Reference Data between Groups

An initial MANOVA examined group differences for QST parameters. A significant multivariate effect was obtained, Pillai's trace V=1.38, $F(39,102) = 2.23$, $p = .001$. As shown

in figure 2, separate univariate ANOVA's revealed significant group differences for WDT $F(3,44) = 5.802$, $p = .002$, $\acute{\eta}_p^2 = .283$, MDT $F(3,44) = 3.559$, $p = .022$, $\acute{\eta}_p^2 = .195$ and WUR $F(3,44) = 3.137$, $p = .035$, $\acute{\eta}_p^2 = .176$

Figure 2.

Mean Z-scored data of all 13 QST parameters for High, Above average, Average, and Low AQ groups



Note. This figure demonstrates the *Z*-score data for each AQ (Autism Quotient) group across all 13 QST parameters including standard error bars. * Indicates significant group differences. Any column that extends outside the 95% confidence interval of the normal distribution of healthy subjects (=area between the black lines) signifies sensory changes. Cold Detection Threshold (CDT), Warm Detection Threshold (WDT), Thermal Sensory Limen (TSL), Paradoxical Heat Sensations (PHS), Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Mechanical Detection Threshold (MDT), Mechanical Pain Threshold (MPT), Mechanical Pain Sensation (MPS), Dynamic Mechanical Allodynia (DMA), Wind-Up Ratio (WUR), Vibration Detection Threshold (VDT) and Pressure Pain Threshold (PPT).

A series of post hoc Tukey analyses was performed to examine group comparisons across all four AQ groups and WDT, MDT, and WUR. Results revealed, in the first instance, that the 'average AQ' group required a significantly lower temperature (M = 33.486°C) to detect warmth than all other groups ($p < .05$; 'high AQ' M = 34.256°C, 'above average AQ' M = 35.031°C and 'low AQ' M = 35.136°C).

Secondly, they revealed that individuals in the 'high AQ' group required a significantly ($p < .05$) greater force (M = 8.280mN) to detect light touch compared to those in the 'average AQ' group (M = 2.537mN) but did not significantly differ to those in the 'low AQ' (M = 4.796mN) or above average AQ groups (M = 5.050mN).

Lastly, the increase in intensity for a 10 series train relative to a single pinprick stimulus of 256mN (WUR) was significantly greater ($p < .05$) in the 'above average AQ' (M = 3.186) group compared to the 'low AQ' group (M = 1.614). They did not significantly differ ($p > .05$) to either the 'high AQ' (M = 2.321) or the 'average AQ' (M = 2.012) groups (see table 2 for descriptives).

Table 2:

Untransformed data values of QST parameters given for each AQ quartile group

Parameter	High AQ	Above average AQ	*Average AQ*	*Low AQ*	*p value*	*Effect size*
QST parameter						
CDT (˚C)	30.400 (0.653)	28.523 (3.658)	28.038 (8.465)	29.790 (2.468)	.686	$\acute{\eta}_p^2$ = .036
WDT (˚C)*	34.256 (0.601)	35.031 (1.350)	33.486 (0.468)	35.136 (1.833)	.001	$\acute{\eta}_p^2$ = .336
TSL (˚C)	7.438 (8.067)	7.705 (5.281)	4.413 (2.776)	5.275 (2.820)	.150	$\acute{\eta}_p^2$ = .123
PHS (n)	0.230 (0.832)	0.31 (0.630)	0.230 (0.832)	0.080 (0.277)	.397	$\acute{\eta}_p^2$ = .071
CPT (˚C)	18.031 (8.432)	16.100 (8.599)	11.085 (10.808)	15.887(10.705)	.183	$\acute{\eta}_p^2$ = .113
HPT (˚C)	42.531 (2.736)	43.974 (2.747)	40.637 (12.453)	41.962 (4.723)	.295	$\acute{\eta}_p^2$ = .087
MDT (mN)+*	8.280 (10.430)	5.050 (5.407)	2.537 (1.643)	4.796 (7.734)	.034	$\acute{\eta}_p^2$ = .193
MPT (mN)+	41.927 (34.044)	87.240 (84.647)	88.427 (191.873)	1.965 (4.652)	.728	$\acute{\eta}_p^2$ = .032
MPS (PR)+	7.538 (15.033)	2.314 (5.630)	2.793 (3.181)	6.241 (10.875)	.720	$\acute{\eta}_p^2$ = .033
DMA (PR)+	0.182 (0.296)	0.183 (0.275)	0.104 (0.011)	1.965 (4.652)	.592	$\acute{\eta}_p^2$ = .046
WUR (PR)+*	2.321 (2.136)	3.86 (2.852)	2.012 (0.832)	1.614 (0.359)	.028	$\acute{\eta}_p^2$ = .201
VDT (/8)	7.013 (1.090)	7.154 (1.059)	7.487 (0.538)	7.359 (0.855)	.841	$\acute{\eta}_p^2$ = .020
PPT (kPa)+	477.077 (257.317)	438.974 (130.282)	475.309 (175.208)	389.333 (146.754)	.426	$\acute{\eta}_p^2$ = .067
Additional Sensory Tests						
CP threshold (s)	8.649 (6.022)	12.499 (6.156)	11.021 (5.161)	12.448 (12.616)	.586	$\acute{\eta}_p^2$ = .037
CP tolerance (s)	35.982 (44.776)	52.095 (43.231)	40.777 (31.898)	41.604 (48.864)	.804	$\acute{\eta}_p^2$ = .020
Elect (mA)	1.960 (0.734)	4.999 (2.920)	3.723 (2.896)	6.305 (1.878)	.027	r = .324

Note. Group raw data values for each QST parameter and additional sensory tests given as mean (*SD*) to aid understanding in terms of their actual unit of measurement i.e., temperature in Celsius.

All p values and effect sizes given for QST parameters are for the inferential statistics conducted on transformed data as discussed in the methods section.

+values are presented as geometric means.

*p<.05.

✝ Non-parametric Mann-Whitney U conducted for these parameters as they did not meet assumptions, all other parameters met parametric assumptions and therefore independent samples t-test conducted.

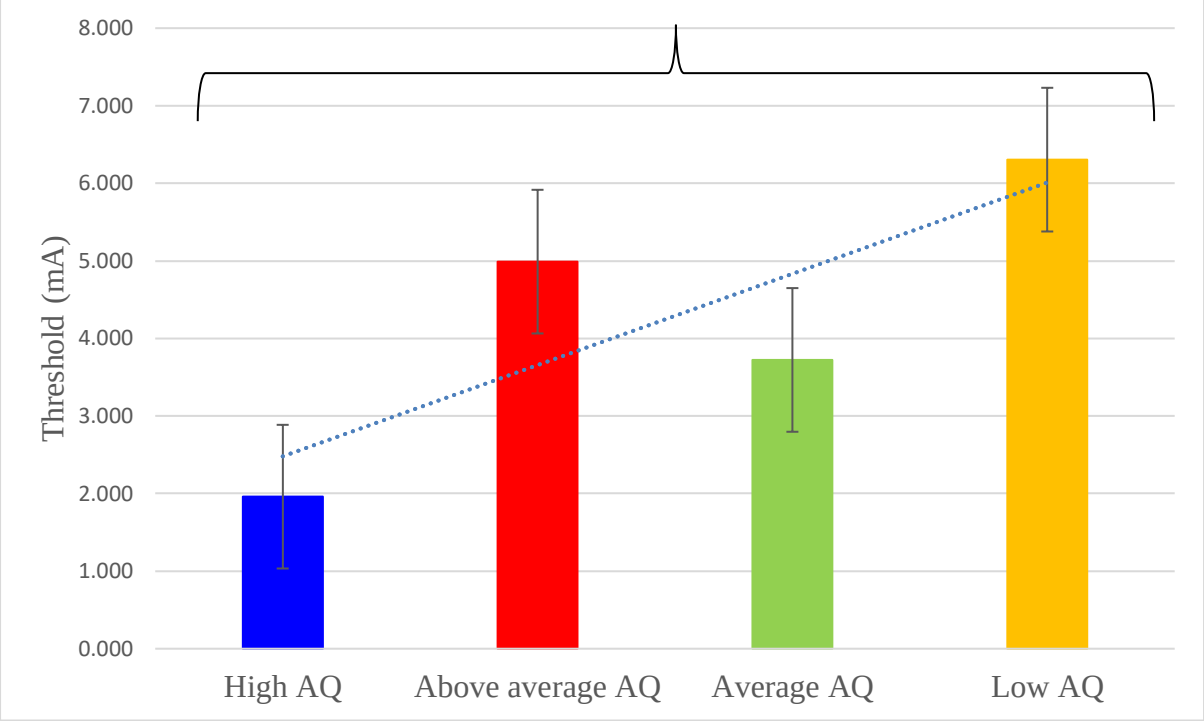
Cold Detection Threshold (CDT), Warm Detection Threshold (WDT), Thermal Sensory Limen (TSL), Paradoxical Heat Sensations (PHS), Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Mechanical Detection Threshold (MDT), Mechanical Pain Threshold (MPT), Mechanical Pain Sensation (MPS), Dynamic Mechanical Allodynia (DMA), Wind-Up Ratio (WUR), Vibration Detection Threshold (VDT), Pressure Pain Threshold (PPT), Cold Pressor (CP) and Electrical (Elect).

2A.3.2 Additional Sensory Tests

With the exception of electrical pain where 17 participants reached the maximum current of the machine without reporting pain, all data values were obtained. There was no significant group differences for cold presser threshold ($F(3,51) = .652$, $p = .586$, $\acute{\eta}^2 = .037$) or tolerance ($F(3,51) = .329$, $p = .804$, $\acute{\eta}^2 = .020$). Electrical pain data did not meet the assumption of homogeneity $F(3,31) = 8.173$, $p = .000$, therefore non-parametric equivalent was conducted; Kruskal-Wallis test. Electrical pain threshold was significantly affected by AQ group $H(3) = 8.601$, $p = .027$. Jonckheere's test revealed a significant trend in the data (see figure 3); as AQ scores increased lower currents were required to achieve a pain threshold, $J = 286.00$, $z = 1.932$, $r = 0.327$ (representing a medium effect). The group differences are depicted in figure 3; the thresholds were lowest in the 'high AQ' group (M = 1.960mA) and highest in the 'low AQ' group (M = 6.305mA). However, the largest number of individuals who reported no pain for electrical stimulation resided in the 'high AQ' group ($n = 9$).

Figure 3.

Mean electrical pain threshold values (mA) for High, Above average, Average, and Low AQ groups



Note. Group data for electrical pain threshold given as milliamps (mA). Including standard error bars and trend line, representing that as Autism Quotient (AQ) traits increased lower current were required to achieve a pain threshold. * indicates significant group differences.

2A.3.3 Avoidance Scores for Pinprick Stimuli including Stimulus/response Function (MPS/DMA)

A non-significant MANOVA showed that there were no group differences for MPS, DMA and WUR avoidance scores, Pillai's trace V=.213, $F(9,111) = .942$, $p = .492$. Follow-up univariate ANOVAs were also non-significant to the value $p>.05$. Correlational analysis between QST parameters and respective avoidance scores were significant. As QST pain-rating value increased so did the desire to avoid feeling, the stimuli (see table 3).

Table 3:

Correlation matrix for QST parameters and matching self-reported avoidance scores

		1	2	3	4	5	6
1.	MPS avoidance	1.00					
2.	DMA avoidance	.465**	1.00				
3.	WUR avoidance	-.279*	-.120	1.00			
4.	MPS	.921**	.429**	-.338**	1.00		
5.	DMA	.543**	.883**	-.173	.532**	1.00	
6.	WUR	-.216	-.097	.766**	-.271*	-.132	1.00

Note. Correlations between mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA) and wind-up ratio (WUR) and the respective avoidance values. Note: ** $p<.001$, *$p<.05$.

2A.3.4 QST Profiles of *Z*-transformed Data in Selected Participants

Overall, there were a greater number of *Z*-scores that fell outside of the 95% confidence levels within the total sample than would be expected by chance (see figure 4; *n* = 100, allocated to 43 of the 52 individuals). For a sample of this size, with 13 QST parameters, 95% confidence interval (CI) levels would estimate that 34 abnormal values would lie outside the 95% CI level of The DFNS reference data. This variance is driven by the larger number of abnormal *Z*-scores in the 'high AQ' and 'above average AQ' groups (*n* = 29 for each group, allocated to 12 of the 13 individuals in each group). In the 'low AQ' there were 26 abnormal *Z*-scores, allocated to 9 of the 13 individuals in the group. The 'average AQ' group had only 16 abnormal *Z*-scores, which was allocated to 10 of the 13 individuals in the group.

Intra-individually, 95% CI dictates that one *Z*-score in the 13 QST parameters would potentially be outside this level, therefore only 26 of our participants are showing atypical QST profiles (where number of *Z*-scores outside the 95% CI >=2). The number of individuals with *Z*-scores outside the CI level of The DFNS reference data, was split across the four AQ quartile groups, however, the number of *Z*-scores per individual varied between the groups (see table 4 for descriptive statistics).

Table 4:

Number of participants with atypical QST patterns and the mean number of abnormal Z-scores of each participant

	High AQ	**Above average AQ**	**Average AQ**	**Low AQ**	**Total**
No. of participants	7	6	6	7	26
Abnormal *Z*-scores	3.429 (1.134)	3.833 (0.983)	2 (0)	3.667 (1.397)	3.192 (1.201)
Range of abnormal *Z*-scores	2-5	3-5	2-2	2-6	2-6

Note. n = total number of participants in each group showing abnormal values (where number of abnormal values >=2; i.e., are outside the 95% CI of the reference data). The number of abnormal values per individual in the groups is given as a mean ± *SD*, and range. Autism Quotient (AQ).

Furthermore, six participants showed sensory distinctive features in the form of paradoxical heat sensations; experiencing a warm, hot, or painfully hot sensation in response to the cold stimulation, that usually do not occur in healthy subjects. Another four individuals felt allodynia to non-painful stimuli, although no significant group differences were reported for either of these $F(3,44) = .268$, $p = .848$, $\acute{\eta}_p^2 = .018$, and $F(3,44) = .787$, $p = .505$, $\acute{\eta}_p^2 = .051$, respectively.

Figure 4.

Adjusted Z-score values for each participant across all 13 QST parameters. This figure demonstrates the pattern of responses for individuals in each of the AQ groups; high, above average, average, and low AQ.

***Fig 4A**: Adjusted Z-scored individual QST profiles for those in the High AQ group*

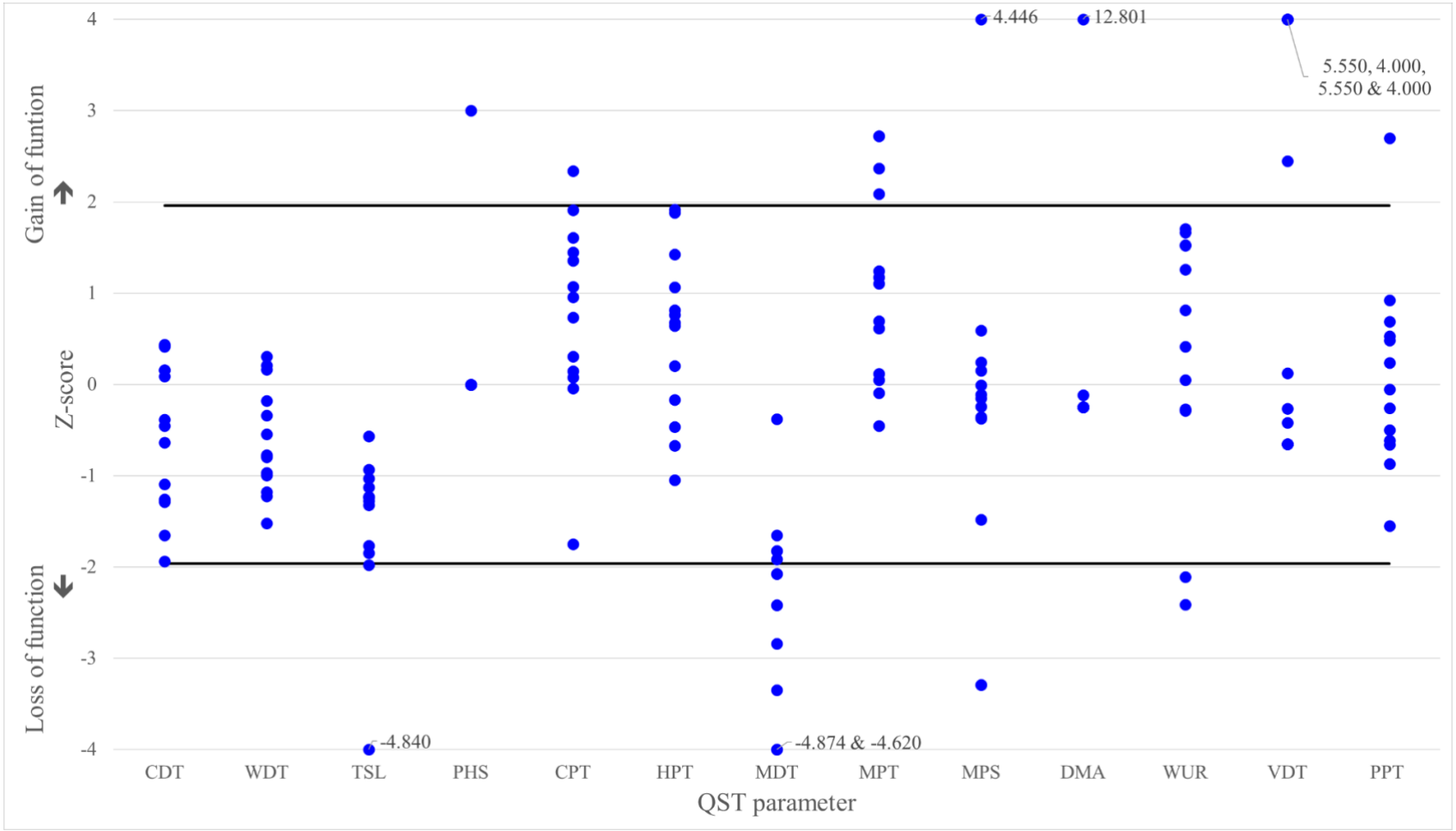


Fig 4B: *Adjusted Z-scored individual QST profiles for those in the Above average AQ group*

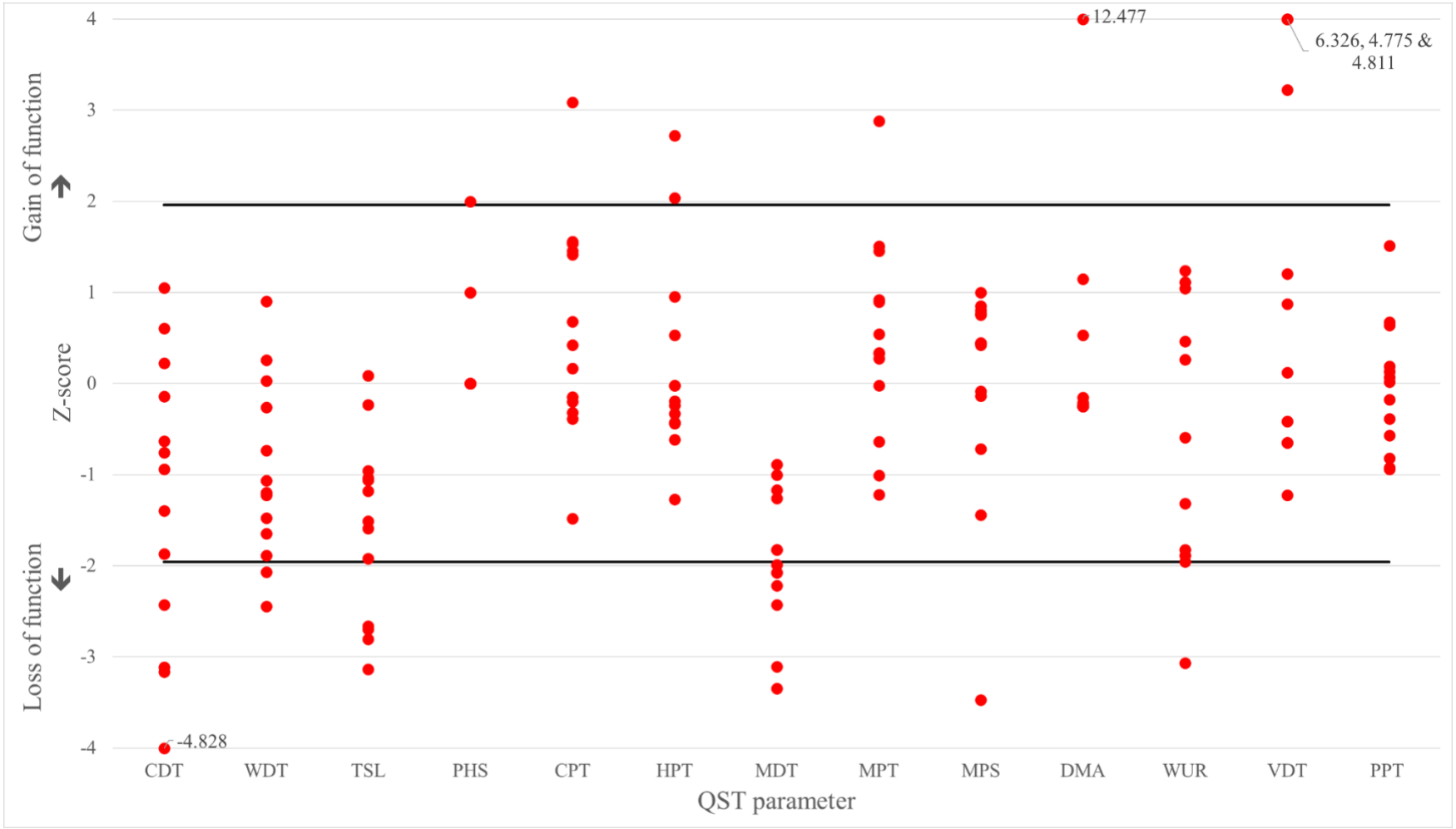


Fig 4C: *Adjusted Z-scored individual QST profiles for those in the Average AQ group*

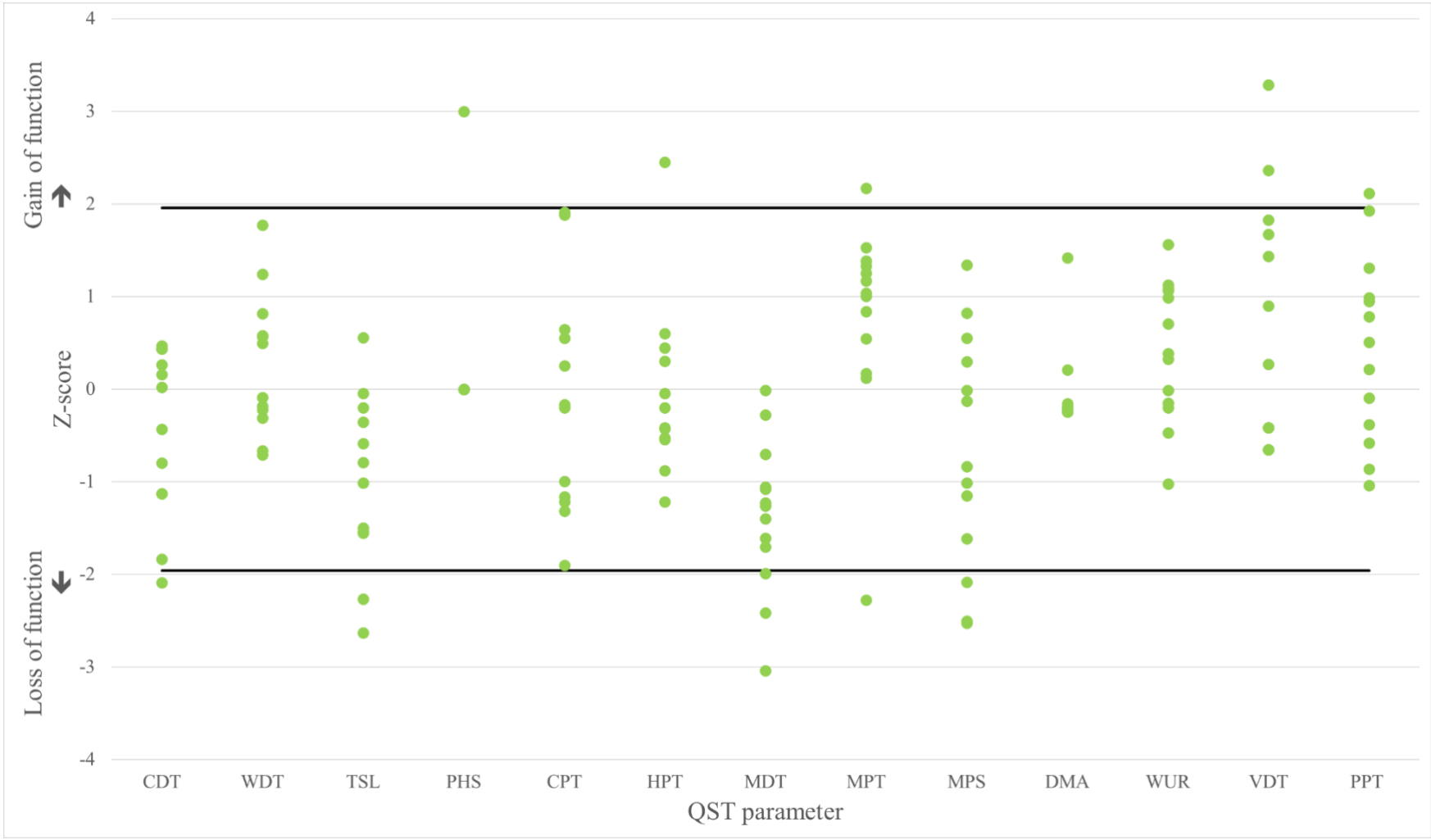
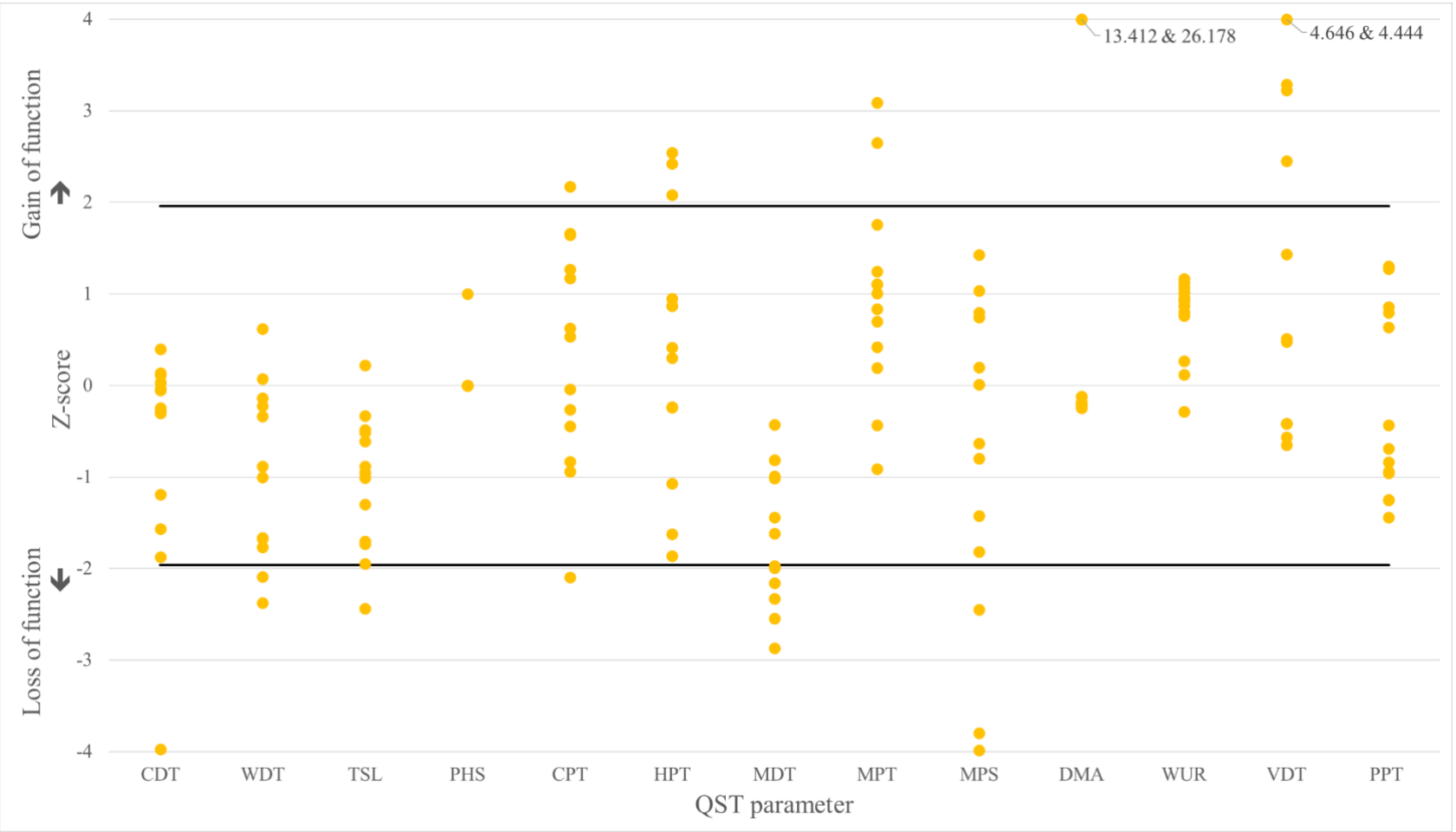


Fig 4D: *Adjusted Z-scored individual QST profiles for those in the Low AQ group*



Note. Individual results of QST parameters are given as *Z*-scores split into AQ quartile groups. Any markers that extend outside the 95% confidence interval of the normal distribution of healthy subjects (=area between the black lines) signifies sensory changes. Cold Detection Threshold (CDT), Warm Detection Threshold (WDT), Thermal Sensory Limen (TSL), Paradoxical Heat Sensations (PHS), Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Mechanical Detection Threshold (MDT), Mechanical Pain Threshold (MPT), Mechanical Pain Sensation (MPS), Dynamic Mechanical Allodynia (DMA), Wind-Up Ratio (WUR), Vibration Detection Threshold (VDT) and Pressure Pain Threshold (PPT).

2A.4 Discussion

The current experiment investigated the utility of a battery for somatosensory perception in a sample of the general population. In order to determine use within a later clinically diagnosed sample, the general population were split by autistic trait severity. For this reason, and to allow the comparison to published norms, 52 adults, underwent the standardised and normed QST protocol (DFNS: Rolke, Baron, et al., (2006)). No observable consistent pathological QST pattern suggesting a defined nerve fibre dysfunction in relation to autistic trait severity, was found.

Group differences were found, however for both warm detection threshold (WDT), mechanical detection threshold (MDT; von Frey filaments), wind-up ratio (WUR; pinprick stimuli) and electrical pain. Only, in the case of MDT did the threshold for high autistic traits group exceed that of the normal distribution of healthy individuals, as established by The DFNS (Backonja et al., 2013; Rolke, Baron, et al., 2006), indicating a clinically significant degree of sensory loss. A possible explanation of this sensory loss is atypical Aβ-fibre function, however considering normal *Z*-scores in other clinically related QST parameters – such as vibration – this must be interpreted with caution. Additionally, within a healthy population order effects across mechanical tests have been reported (Gröne et al., 2012), albeit with inconsistencies in which tests are affected. Findings for MDT are in line with Fründt et al., (2017) who similarly report a significant loss of function for mechanical detection using the same standardised testing from the QST battery, however this was in a clinical sample of autistic individuals. Supporting the notion that Aβ-fibre function is altered in ASD.

Additionally, electrical pain thresholds were lowest in the 'high AQ' group and highest in the 'low AQ' group, adding a further confound to interpreting these findings.

These findings also differ compared to both Yasuda et al., (2016) and Bird et al., (2010) who report normal electrical pain. However, these studies were conducted in clinical populations of ASD, site of stimulation differed, as did the range of stimulation applied. Yasuda et al., (2016) used a similar method of limits though their stimulation range had a maximum upper limit of 256μA but did not mention the site of stimulation. Our lowest AQ group's pain threshold was 6.305mA which would suggest that their methodology was restrictive. Having a broader range of stimuli appears to have encapsulated significant group differences. Contrary to Bird et al., (2010) who stimulated the dorsum of the hand, site of stimulation in our experiment was the ventral forearm, directly accessing the median nerve (Backes et al., 2000; Burke et al., 1975; Kazamel & Warren, 2017; McGlone & Reilly, 2010). A potential explanation for the sensitivity observed here, is that the ASD group had greater startle potentiation to a negative stimulus as a result of the activation of the median nerve (Wilbarger et al., 2009). However, electrical pain is also known to affect the membrane potential of all cells leading to the activation of all receptors, resulting in a complex sensation (Lee et al., 2000), including Aβ-fibres at lower intensities and Aδ and eventually c-fibres (Accornero et al., 1977; Inui & Kakigi, 2012). It is possible that in this instance that there was preferential activation of Aβ-fibres because the stimulus did not reach sufficient intensities to activate all (Accornero et al., 1977). In terms of a further psychophysical explanation for alterations in ASD of electrical pain threshold, further work is needed. Closer inspection of the drop out sample for electrical pain shows that the largest number of individuals who reported no pain resided in the 'high AQ' group, adding further difficulties to interpreting findings. Interestingly, a number of these individuals who dropped out for reporting no pain, had abnormal mechanical detection threshold values. This highlights the importance of measuring MDT in a clinical population of ASD, and that this might be a superior methodology to adopt. Findings indicate that there may be sub populations with

different autistic traits that result in either hypo- or hyper-responsiveness to mechanical and electrical stimulation.

A further phenomenon seen in individuals with abnormal MDT and electrocutaneous pain, was that of DMA. DMA is defined as the experience of perceiving pain from a tangential movement across the skin which is typically innocuous (Buonocore et al., 2016). In particular, the perceiving of an innocuous touch, such as gentle stroking, as aversive has been described in sensory over-responsivity research (Baranek et al., 1997; Green et al., 2016; Reynolds & Lane, 2008). This is a phenomenon which does not normally occur in individuals otherwise considered healthy, but which supports the idea of Aβ-fibre function abnormalities, as it has been attributed to the activation of these mechanoreceptors (Buonocore et al., 2016; Li et al., 2011). Central sensitization i.e., changes in signalling in the spinal cord (Campbell & Meyer, 2006), is commonly thought to underlie DMA (Gierthmühlen et al., 2012), as it is the increased response of neurons to stroking stimuli i.e. dynamic stimuli. Furthermore, participants with higher autistic traits reported greater intensity for wind-up ratio. Wind-up ratio refers to the progressive increase in the magnitude of evoked responses (Li et al., 1999). There is then an increase in the excitability of spinal cord neurons which arises due to slow temporal summation of evoked responses of C-fibres (Herrero et al., 2000; Li et al., 1999; Uhl et al., 2011). Wind-up ratio is also thought to lead to characteristics of central sensitization such as expansion of receptive fields and enhanced response to C-fibre stimulation (Li et al., 1999). It must be noted however, that this later finding was only the case for those in the above average AQ group. These findings, paired with the dearth of research considering central sensitization in autism show it to be an important factor to investigate further within autism, therefore highlighting the utility of investigating DMA and WUR in a clinical population.

A notable limitation of this experiment is the use of the Autism Quotient to determine both autistic trait severity and to then split the groups based on this severity. Recently, the AQ and the replication of the proposed structure has come under scrutiny. To date, there have been several different suggestions for dimensions (Hurst et al., 2007; Kloosterman et al., 2011; Lau et al., 2013) from four (Stewart & Austin, 2009) to two (Hoekstra et al., 2007). With the two factor-model confirmed in a validation with a short form of the AQ (Hoekstra et al., 2007). Additionally, if autistic traits are a continuum, properties must be similar among those with and without ASD, however frequently psychometric analyses are based on non-ASD samples alone or general population studies where diagnosis of autism is not accounted for (for review see Lundqvist & Lindner, (2017); Ruzich et al., (2015)). The short form AQ has shown the same underlying traits in both groups (Murray et al., 2014) and more rigorous studies have shown similar findings for the AQ (Ketelaars et al., 2008). Additionally, although methods do differ in terms of the use of PCA to determine dimensions in more recent studies compared to the seminal piece by Baron-Cohen, the AQ has shown both high sensitivity and specificity in a referred sample of individuals being assessed for ASD with an identifying rate of 76% when a cut of score of 32 is used (Baron-Cohen et al., 2001). Within families genetically linked to ASD, the AQ has shown heritability (Hoekstra et al., 2007). In future studies, aiming to gain a measure of autistic trait severity for research purposes, to confirm diagnosis and to check for group differences between controls, the AQ is still a sufficient measure to use. Secondly, as order effects have been reported for the QST battery wherein an increased mechanical perception is the result of preceding thermal testing (as in The DFNS standardised protocol), the battery order may be problematic (Gröne et al., 2012). However, results for this finding are inconsistent across the mechanical modality and to date has only been investigated in healthy individuals. Utilising the standard protocol rather than amending it for use in a clinical population, will allow for comparisons of results to the

published norms and other studies that have utilised this battery; showing that there is utility in this protocol order. Lastly, although the BAP offers valuable insight into plausible genetic and neurobiological pathways and has shown candidate traits including language delay and social deficits that map onto clinical traits of ASD (Sucksmith et al., 2011). It is not a substitute for studies in clinical populations of ASD. The nuances and range of clinical traits in ASD that differ to those currently thought to belie BAP (Sucksmith et al., 2011), alongside the heterogeneity of ASD means it is important to conduct such tests in clinical samples.

To conclude, there was no evidence towards a systematic alteration suggesting underlying dysfunction in somatosensory modalities linked to autism trait severity. Electrical pain stimulation may not be a useful test due to the complexity of activation and therefore may not be suitable in a clinical sample of ASD. QST, is a useful and appropriately sensitive battery to use in a clinical population, particularly to investigate the role of central sensitization alongside Aβ-fibre function using appropriately more sensitive tests. There is further utility in this battery in that it can provide a comparison to published norms, which will result in clearer comparisons to clinically significant thresholds over and above the traditional group comparison.

Chapter 2B. A Quantitative Sensory Testing Approach to Pain in Autism Spectrum Disorders

The following Experiment 2 has been published in The Journal of Autism and Developmental Disorders (see Appendix A) and is presented in line with the Author Archiving and Re-Use guidelines, namely that it is verbatim to the published work. Upon request by the examiners, this also includes some minor additions.

Chapter 2B. Experiment 2

2B.1.2 Rationale

This experiment will similarly employ the standardised battery, conducting an independent replication of (Fründt et al., 2017) and utilise the published normative reference values (Rolke, Magerl, et al., 2006) as they provide a determinant of sensory loss and gain that supersedes the standard group differences analysis - meaning clinically significant sensitivities in ASD can be determined. Furthermore, this battery was extended to include a measure of pain tolerance and central pain processes, utilising the cold pressor test (von Baeyer et al., 2005) and Conditioned Pain Modulation (CPM; Yarnitsky et al., (2015)), respectively. Including tolerance allows a wider range of psychophysics to be measured; threshold (the minimum intensity of a stimulus that is perceived as painful), suprathreshold (increases the frequency of nociceptive messages) to tolerance (the maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation (Chapman et al., (1985); *IASP Terminology - IASP*, (2017)). Tolerance also includes additional components such as pain motivation; to quantify said motivation; self-reported desires to avoid pain were measured. CPM represents one type of central pain process; that of descending spinal modulation, that although not currently tested in ASD populations, is a paradigm easily implemented in a laboratory setting. It is a process whereby one noxious stimulus inhibits the perception of a second noxious stimulus, where greater reductions in pain are thought to reflect greater pain inhibitory capacity (Martel et al., 2013; Nir & Yarnitsky, 2015). The addition of each will give insight into tolerance, pain motivation, and central pain processes in ASD.

2B.2 Methods

2B.2.1 Participants

Twenty-six adults (14 males) covering an age range between 18 and 52 years were recruited (M = 27.15, SD = 8.50) to this case-control experiment. ASD participants were recruited from a specialist diagnostic service within a local hospital trust and had received a diagnosis based on the DISCO (Diagnostic Interview for Social and Communication Disorders) and/or ADOS (Autism Diagnostic Observation Schedule) from a trained clinician. Diagnosis letters were obtained from participants where possible, which confirmed diagnosis and IQ values >70. Those suffering from chronic pain, eczema, epilepsy, or asthma were excluded. Additionally, any with a reported history of a psychiatric disorder or learning disability were excluded. Thus, 13 ASD participants were included in the experiment; there were seven males and six females with a mean age of 27.22 years (SD = 9.19). No participant reported any medication use for depression or anxiety, although one reported the use of Amlodipine and one reported the use of Lansoprazole.

Thirteen control participants without a diagnosis of ASD were recruited through advertisement, selected to match each autistic individual on age (M = 27.08, SD = 8.129) and gender (7 males). All were subject to the same exclusion/inclusion criteria above. Although not explicitly matched on IQ, the control group were from the general population, suggesting IQ>70. All participants in both groups were without pain medication or alcohol at least 24 hours before the investigation.

As groups (n = 13 per group) were age and gender matched they did not significantly differ; $t(22) = -.045$, $p = .964$ and $\chi^2(1) = 0$, $p = .652$, respectively. As expected groups had significantly different AQ score (Autism Quotient: (Baron-Cohen, Wheelwright, Skinner,

Martin, & Clubley, 2001) scores, $t(24) = -6.003$, $p = .000$, with the ASD group scoring higher (see table 5 for descriptive statistics).

Table 5:

Characteristics and questionnaire results of ASD and control group

Characteristic		ASD	Controls	Total
No. of participants		13	13	26
No. of participants with	ASD	1	-	1
	HF autism	2	-	2
	Asperger's	10	-	10
Age		27.22 ± SD 9.19	27.08 ± SD 8.13	27.15 ± SD 8.50
Gender Female		6	6	12
Male		7	7	14
Autism Quotient (AQ)		32.00 ± SD 6.58	15.38 ± SD 7.50	23.69 ± SD 10.94

Note. All values are given as mean ± *SD*. **p*<.05. HF (high functioning) and ASD (Autism Spectrum Disorder).

The experiment was approved by Liverpool John Moores Ethics Committee (REC ref: 15/NSP/023) and NHS Health Research Authority ethics committee (Ref: 16/EM/0402) and all participants gave written informed consent.

2B.2.2 Procedure and Design

To quantify self-reported autistic trait severity participants completed the AQ (Baron-Cohen et al., 2001). QST was performed first. This standardized battery provides a sensory profile that consists of 13 parameters (see table 6, Rolke, Magerl, et al., 2006). Additional cold pressor and CPM tests were added to the battery and all tests were performed in the same order, using the same set of standardised instructions, and performed on the same site on each participant.

2113 ***Table 6:***
2114 *Details of Standardised Quantitative Sensory Testing battery, tests and associated peripheral*
2115 *sensory channel*

Group No.	Description	Test (Abbreviation)	Peripheral sensory channel
1.	Thermal detection thresholds for the perception of cold, warm and paradoxical heat sensations. Performed using a Medoc Pathway stimulator, ramped stimuli 1°C/s, baseline temperature 32°C and a 9cm² Thermode.	Cold detection threshold (**CDT**) Warm detection threshold (**WDT**) Paradoxical heat sensations (**PHS**) Thermal sensory lumen (**TSL**)	A-delta C C, A-delta C, A-delta
2.	Thermal pain thresholds for cold and hot stimuli (as above).	Cold pain threshold (**CPT**) Heat pain threshold (**HPT**)	C, A-delta C, A-delta
3.	Mechanical detection thresholds for touch and vibration. Performed using a modified set of von Frey hairs (0.25 to 512mN) with 5 ascending and 5 descending stimulus intensities and a 64Hz tuning fork (8/8).	Mechanical detection threshold (**MDT**) Vibration detection threshold (**VDT**)	A-beta A-beta
4.	Mechanical pain sensitivity, including thresholds for pinprick, stimulus-response functions for pinprick sensitivity, dynamic mechanical allodynia and pain summation to repetitive pinprick stimuli. Performed using a set of weighted pinpricks that exert forces of 8, 16, 32, 64, 128, 256 and 512mN.	Mechanical pain threshold (**MPT**) Mechanical pain sensitivity (**MPS**) Dynamic mechanical allodynia (**DMA**) Wind-up ratio (**WUR**)	C, A-delta C, A-delta C, A-delta C, A-delta
5.	Pressure pain threshold. Performed using an algometer with a 1cm² probe area, where stimulus intensity is gradually increased at a ramp rate of 50kPa.s.	Pressure pain threshold (**PPT**)	C, A-delta
6.	Cold pain threshold and tolerance. Performed with a custom cold pressor which maintains water at 2°C, participants submerge their dominant hand in the water stating "pain" for threshold and tolerance is measured as the point at which the hand is voluntarily removed.	Cold pressor test	C, A-delta
7.	Pain modulation. Performed using an algometer with a 1cm²-probe area, where stimulus intensity is gradually increased at a ramp rate of 50kPa/s and a cold pressor test (see 6.)	Conditioned Pain Modulation **(CPM)***	-

Test order: Cold and warm thermal detection thresholds are acquired first followed by paradoxical heat sensations during thermal sensory lumen of alternating warm and cold stimuli (no.1). Cold and heat thermal pain thresholds (no.2) are then determined. Then follows; mechanical detection (no.3), mechanical pain (no.4), stimulus/response functions with dynamic mechanical allodynia (no.4), wind-up ratio (no.4), vibration (no.3), pressure pain (no.5), cold pressor test (no.6) and lastly conditioned pain modulation (no.7) is performed.
Darker grey shaded boxes show additional tests that are not part of The DFNS QST battery (i.e., no. 6 & 7).
*This is a measure of central pain processes not of the peripheral sensory channels; although these channels are involved in the initial detection of the relevant stimuli (see no. 4 and 5).

2B.2.2.1 Cold Pressor Test

A custom cold pressor (Dancer Design), which maintains water in a stimulus tank at a predefined temperature (2°C), measured both cold pain tolerance and threshold. A control unit containing a temperature controller drives water taken from a reservoir of ice water (maintained at 0°C) through the stimulus tank at a controlled rate, therefore, maintaining the requested temperature within 0.10°C.

Pain threshold is defined as the elapsed time between arm immersion and the first report of a pain sensation. Pain tolerance is defined as the elapsed time until the hand is voluntarily removed. Since the Cold Pressor test induces pronounced sympathetic activation and vasoconstriction, the maximum duration of limb immersion was set at 3 minutes (Mitchell et al., 2004).

2B.2.2.2 Conditioned Pain Modulation (CPM)

To assess CPM baseline pressure pain thresholds (PPT) was firstly performed on the right upper trapezius, approximately 2 cm from the acromioclavicular joint with a handheld pressure algometer (Somedic) with a $1cm^2$ probe area. The threshold was determined with an ascending stimulus intensity, applied as a slowly increasing ramp of 50kPa/s until participants report a painful sensation. Immediately following the assessment of PPT, participants underwent a cold pressor test, immersing their hand up to the wrist in a stimulus tank of 2°C water. Twenty seconds following hand immersion, PPT was re-assessed on the right trapezius (i.e., the same site as baseline assessment).

2B.2.2.3 Avoidance and Motivation Scores for Pinprick Stimuli including Stimulus/response Function (MPS/DMA)

Pain experience is more than just the sensory experience, the functional purpose of pain is to create a motivational state to avoid future harm (Eccleston & Crombez, 1999). To measure the motivation to avoid experiencing painful stimuli, participants were asked that, for every stimulus that was given a pain rating (a value above 0 on a numeric rating scale of 0 – 100 where 0 means no pain and 100 means the most intense pain imaginable, any figure over 0 is considered to be a rating of pain: see the QST supplementary materials for MPS, DMA and WUR) during Mechanical Pain Sensation (MPS), Dynamic Mechanical Allodynia (DMA) and Wind-Up Ratio (WUR), to rate how much they would like to avoid feeling that stimulus. Avoidance was rated using the same scale as the aforementioned QST parameters of 0 to 100; 100 being "would never like to experience the stimulus again". MPS avoidance was calculated as the geometric mean of all avoidance ratings for pinprick stimuli, while DMA avoidance was the geometric mean of all avoidance ratings corresponding to the dynamic stimuli. The wind-up ratio avoidance was calculated as the ratio of the mean of the five series avoidance ratings divided by the mean of the five single stimuli avoidance ratings.

2B.2.3 Data Preparation

2B.2.3.1 QST

Preparation of individual participant's data followed the guidance of the DNFS (Rolke, Magerl, et al., 2006). For pinprick (MPS/DMA), as well as their corresponding avoidance measures, a small constant (+0.1) was added prior to log-transformation to avoid a loss of zero rating values (Bartlett, 1947; Magerl et al., 1998).

For each individual's raw scores it has been previously established that all QST data except Paradoxical Heat Sensations (PHS), Cold Pain Threshold (CPT), Heat Pain Threshold

(HPT), and Vibration Detection Threshold (VDT) follow either a logarithmic progression (i.e. stimulus intensity of the pin prick stimuli are 8mN, 16mN, 32mN, …) or that these data always conform to this distribution, therefore individual participants raw scores were logarithmically transformed before creation of mean values for analysis (Magerl et al., 2010; Rolke, Magerl, et al., 2006). To permit normalisation for age, gender and testing site, each individual's QST data were z-transformed by subtracting the mean value of the corresponding published QST reference value followed by a division by the respective standard deviation from the normative database for the appropriate age and gender group; for each QST parameter using the following expression:

$$Z\text{-score} = (X_{\text{single participant}} - \text{Mean}_{\text{norms}})/SD_{\text{norms}}$$

An additional reason for this transformation is that it results in a QST profile where all parameters are presented as standard normal distributions. For clarity and ease, in order to think in terms of gain (lower thresholds or lower intensity stimulus required for detection or pain report) or loss of function (higher thresholds, or greater intensity required for detection or pain report), the algebraic sign of *Z*-score values was adjusted so that it would reflect a participant's sensitivity to this parameter. *Z*-values above "0" indicate a gain of function, when the patient is more sensitive to the tested stimuli, while a score below "0" indicate a loss of function referring to a lower sensitivity. Thus, all required reversing, with the exception of CPT, MPS, DMA and WUR. For PHS and DMA it is a priori impossible to assess a pathological reduction since these signs are normally absent in a healthy population. If the resulting Z score exceeds 1.96, it is outside the 95% confidence interval of the standard normal distribution with zero mean and unit variance, independent of the original units of measurement. An advantage beyond that of establishing whether any participant, neurotypical or ASD, has clinically significant sensory loss or gain, is that of placing all the

data into a standardised space where individuals QST patterns can be explored. This somewhat allows us to navigate the ASD phenotype and look at individual level data.

QST data were re-transformed, and raw values are presented in table 3 as mean ± SD to ease understanding, and so that data could be presented in terms of the individual units of measurement e.g., temperature in ˚C. All inferential statistics for QST were conducted on *Z*-scored data. Where values are presented as *Z*-scores figures and tables state this. All statistical calculations were performed with SPSS.

2B.2.3.2 Additional Sensory Tests

These data did not undergo the same transformation as the QST data. This was to ensure that results were comparable to other published data where possible.

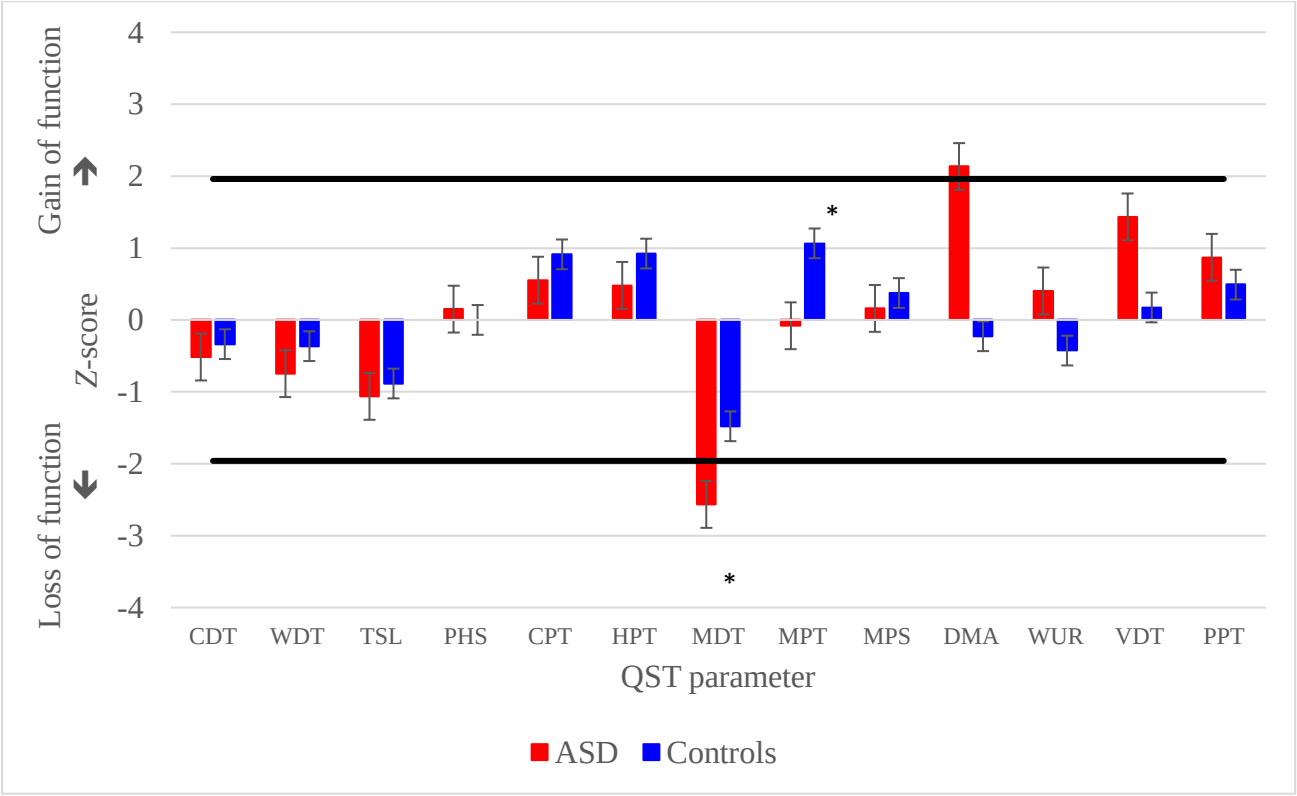
2B.3 Results

It was possible to obtain all QST data in all 26 participants. For one-control participant WUR, avoidance scores could not be calculated because the denominator (mean rating for the single stimulus) was zero.

2B.3.1 QST Reference Data between Groups

Figure 5.

Adjusted Z-scored data of all 13 QST parameters for both ASD and Control group



Note. Adjusted *Z*-score data for ASD vs. control group, across all 13 QST parameters including standard error bars. * indicates significant group differences. Any column that extends outside the 95% confidence interval of the normal distribution of healthy subjects (=area between the black lines) signifies sensory changes. Cold Detection Threshold (CDT), Warm Detection Threshold (WDT), Thermal Sensory Limen (TSL), Paradoxical Heat Sensations (PHS), Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Mechanical Detection Threshold (MDT), Mechanical Pain Threshold (MPT), Mechanical Pain Sensation (MPS), Dynamic Mechanical Allodynia (DMA), Wind-Up Ratio (WUR), Vibration Detection Threshold (VDT) and Pressure Pain Threshold (PPT).

Group comparisons (see figure 5) of each QST parameter's mean Z score, using independent t-tests, revealed a significant difference for mechanical detection and pain threshold (MDT & MPT). The ASD group (M = 8.238mN) required a significantly greater force to detect light touch than the control group (M = 3.267) $t(24) = -3.073$, $p = .005$. They also reported pain at a greater force (M = 125.596mN) for mechanical pain than controls (M = 46.687mN) $t(24) = -2.950$, $p = .007$. The ASD group shows hyposensitivity to mechanical stimuli compared to controls; although only in the case of MDT does this reflect hypoesthesia for mechanical detection (as shown by a value that falls outside the 95% confidence interval of the published reference data).

Table 7:

Untransformed data values of QST test parameters given for ASD and Control group

Parameter (Mean ± Standard Deviation)	**ASD**	**Controls**	***p value***	***Effect size***
QST parameter				
CDT (˚C)	30.423 ± SD .661	30.503 ± SD 1.019	.579	δ = 0.2
WDT (˚C)	34.618 ± SD 1.545	34.092 ± SD .758	.287	δ = 0.5
TSL (˚C)	5.103 ± SD 2.415	4.550 ± SD 1.951	.515	δ = 0.2
PHS (n)	0.150 ± SD 0.555	.	.317†	δ = 0.1
CPT (˚C)	20.615 ± SD 6.651	16.546 ± SD 12.021	.491	δ = 0.3
HPT (˚C)	42.297 ± SD 3.576	40.918 ± SD 2.598	.272	δ = 0.4
MDT (mN)+*	8.238 ± SD 7.638	3.267 ± SD 2.564	.005	δ = 1.2
MPT (mN)+*	125.296 ± SD 157.378	46.687 ± SD 37.438	.007	δ = 1.2
MPS (PR)+	1.860 ± SD 2.382	2.048 ± SD 2.570	.685	δ = 0.2
DMA (PR)+	.863± SD 2.698	.	.379†	δ = 0.4
WUR (PR)+	5.498 ± SD 7.533	2.021 ± SD 2.369	.203	δ = 0.5
VDT (/8)	7.282 ± SD .880	7.744 ± SD .512	.129	δ = 0.8
PPT (kPa)+	307.205 ± SD 60.124	361.846 ± SD 105.572	.162	δ = 0.6
Additional Sensory Tests (Mean ± Standard Deviation)				
CP threshold (s)	12.245 ± SD 7.901	11.284 ± SD 8.891	.773	δ = 0.1
CP tolerance (s)	37.278 ± SD 45.493	28.235 ± SD 17.873	.511	δ = 0.3
CPM1 (kPa)	317.770 ± SD 111.456	345.000 ± SD 95.076	.173	See results
CPM2 (kPa)	428.920 ± SD 202.720	393.46 ± SD 123.799	.173	See results

Note. Group raw data values for each QST parameter and additional sensory tests given as mean ± SD to aid understanding in terms of their actual unit of measurement i.e., temperature in Celsius.
All p values and effect sizes given for QST parameters are for the inferential statistics conducted on transformed data as discussed in the methods section.
+values are presented as geometric means.
*$p<.05$.
† Non-parametric Mann-Whitney U conducted for these parameters as they did not meet assumptions, all other parameters met parametric assumptions and therefore independent samples t-test conducted. Cold Detection

Threshold (CDT), Warm Detection Threshold (WDT), Thermal Sensory Limen (TSL), Paradoxical Heat Sensations (PHS), Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Mechanical Detection Threshold (MDT), Mechanical Pain Threshold (MPT), Mechanical Pain Sensation (MPS), Dynamic Mechanical Allodynia (DMA), Wind-Up Ratio (WUR), Vibration Detection Threshold (VDT) and Pressure Pain Threshold (PPT).

2B.3.2 Additional Sensory Tests

2B.3.2.1 Cold Pressor Test

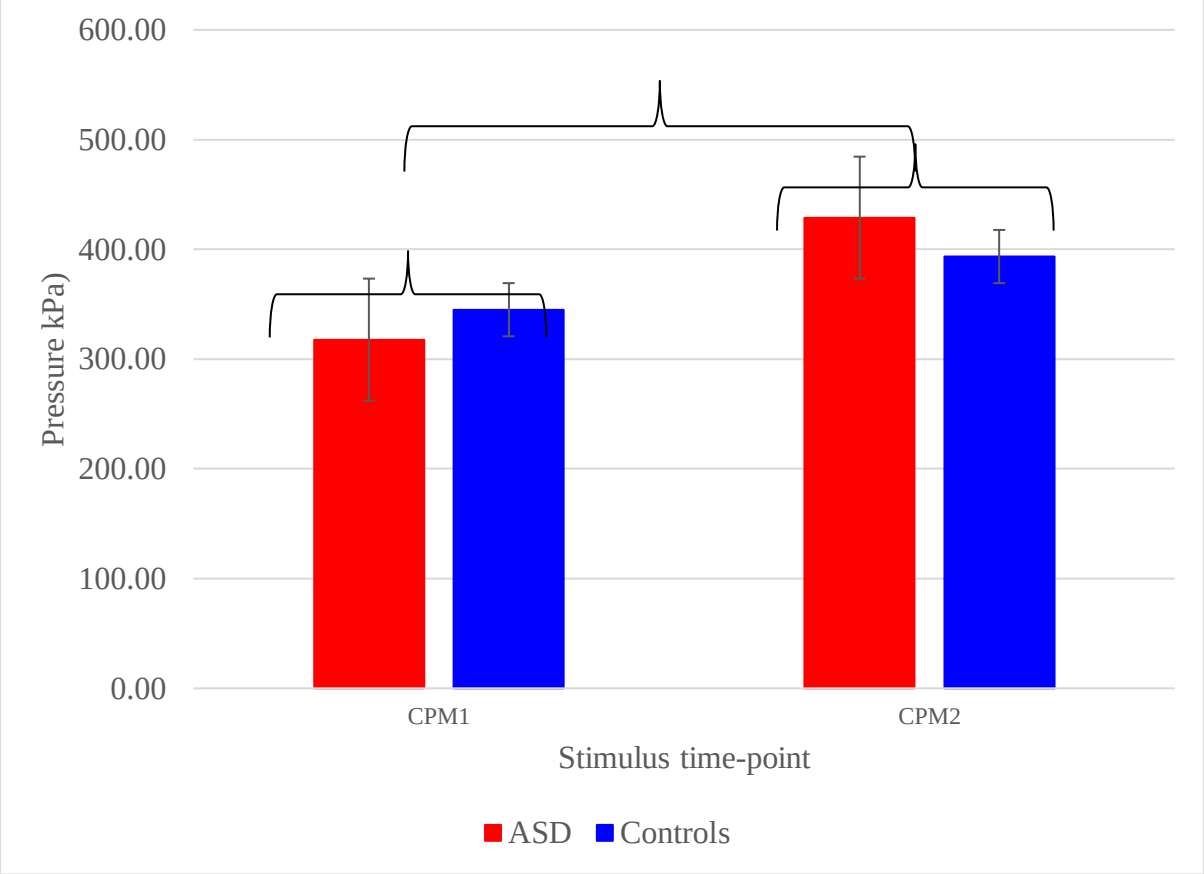
Independent t-tests revealed there were no significant group differences for cold presser threshold or tolerance $t(24) = -.291$, $p = .773$ and $t(24) = -.667$, $p = .511$, respectively (see table 7 for mean values).

2B.3.2.2 Conditioned Pain Modulation

A repeated measures ANOVA revealed that pressure pain was significantly modulated by a cold pressor test $F(1) = 12.793$, $p = .002$, $r = 0.6$, as the pressure pain threshold increased after the hand was submerged for the 20s, across groups, supporting the existence of a CPM effect in the sample. The magnitude of this CPM effect, however, did not significantly differ between groups $F(1) = 1.974$, $p = .173$, $r = 0.2$. Cold pressor pain mediated pressure pain, as shown by the increase in pressure required to elicit a pain response regardless of group (see table 7 for mean values and figure 6 for illustration).

Figure 6.

Mean force for pressure pain (kPA) in the Conditioned Pain Modulation test for ASD and control group



Note. Group data for conditioned pain modulation (CPM), including standard error bars, given as raw data values in kilopascal (kPa). * Indicates significant stimulus time-point differences.

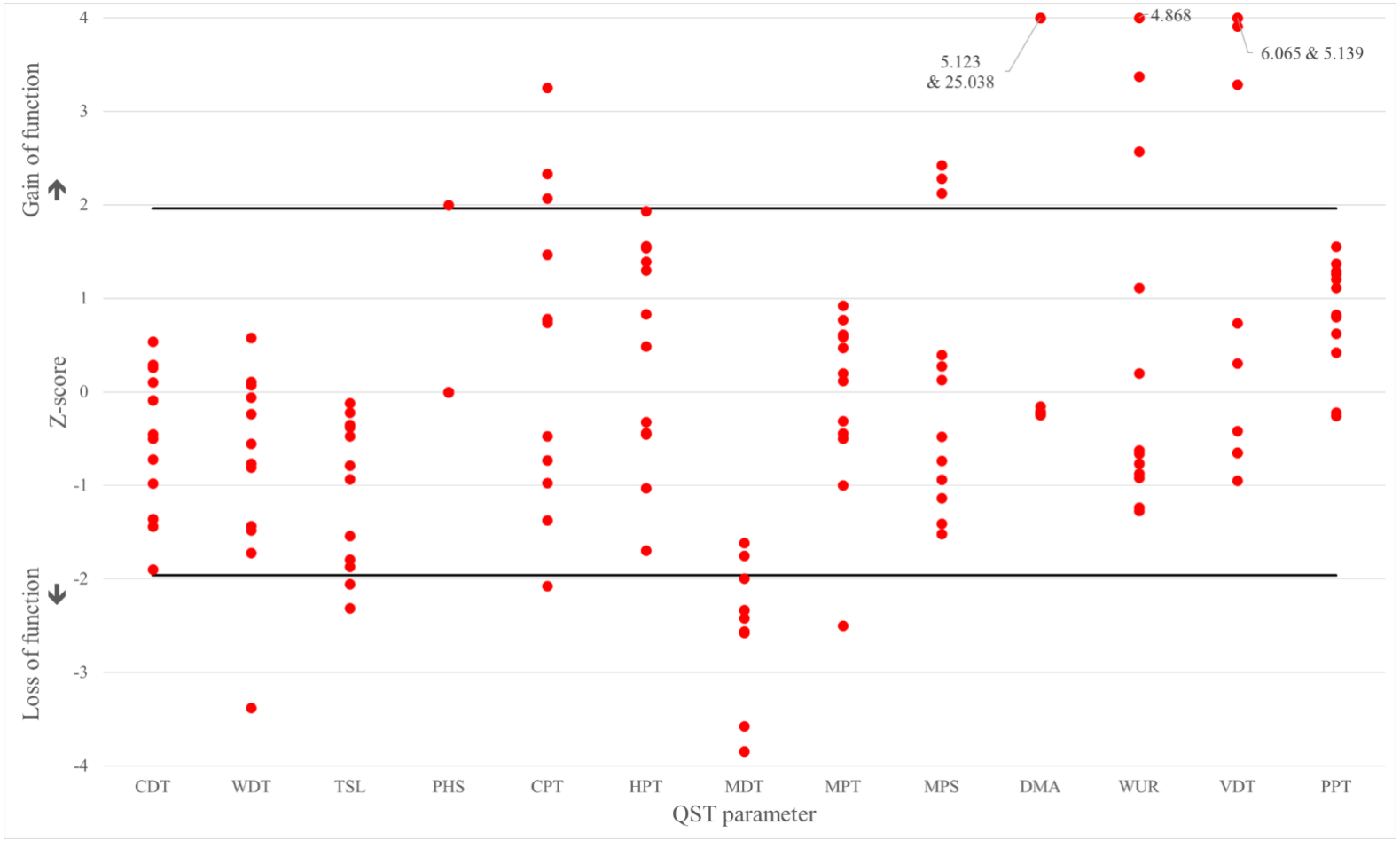
2B.3.3 Avoidance Scores for Pinprick Stimuli including Stimulus/response Function (MPS/DMA)

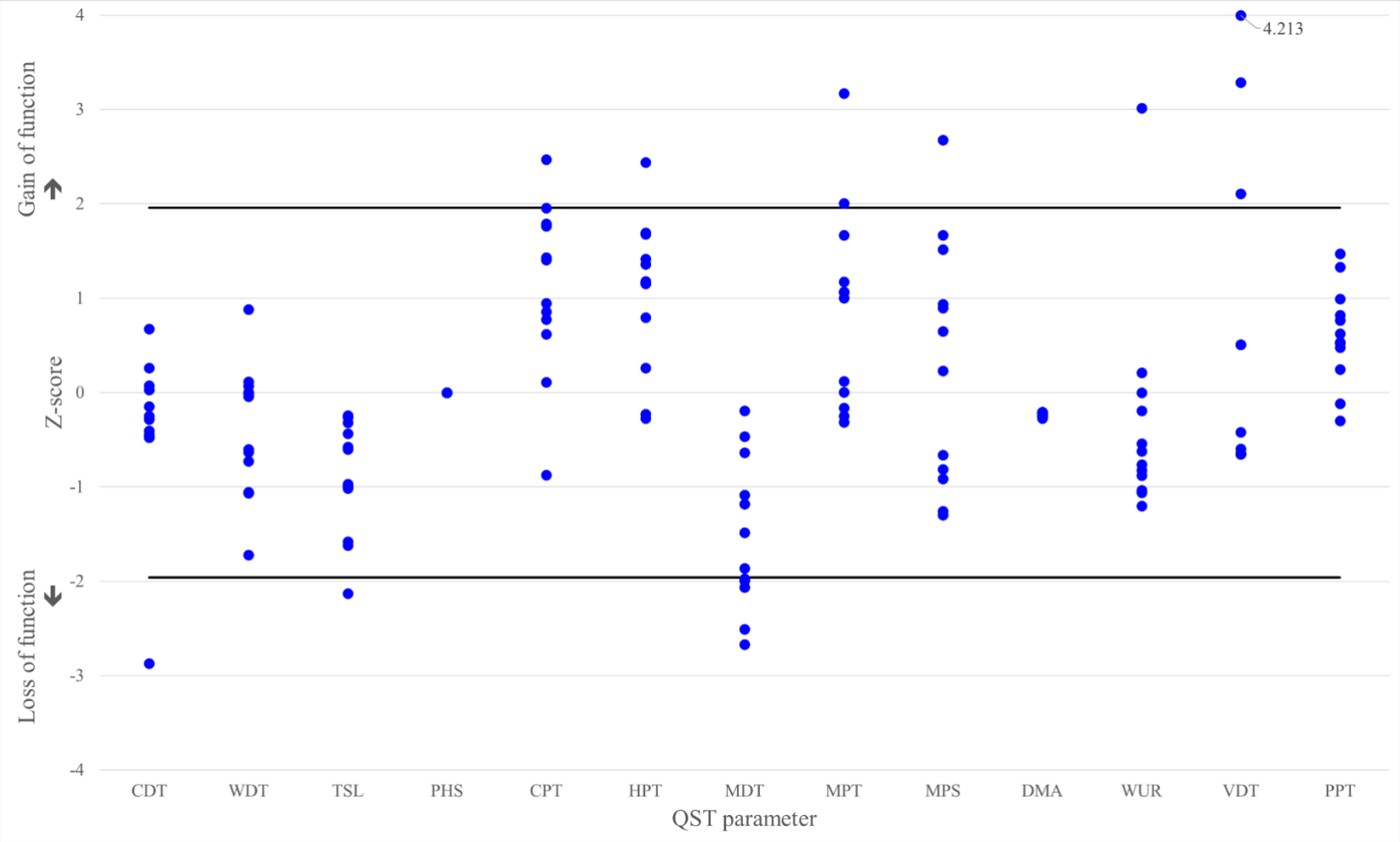
For avoidance scores, *t*-tests were only conducted when parametric assumptions were met; otherwise, Mann-Whitney *U* test was used. There were no group differences for MPS avoidance ($t(24) = -.260$, $p = .797$). Neither DMA nor WUR avoidance differed between groups ($U = 68.000$, $z = -.879$, $p = .194$ and $U = 66.000$, $z = -.958$, $p = .178$).

2B.3.4 QST Profiles of *Z*-transformed Data in Individual Participants

Figure 7.

Z-score values for each participant across all 13 QST parameters. This figure demonstrates the pattern of responses for individuals in the ASD group (red scatter plot) and the Control group (blue scatter plot)





Note. Individual results of QST parameters given as *Z*-scores of autism participants (red) vs. controls (blue). Any marker that extends outside the 95% confidence interval of the normal distribution of healthy subjects (=area between the black lines) signifies sensory changes. Values that extended beyond 4 standard deviations were given a maximum value of 3.999 or -3.999 and true values are given next to the marker. Data were constrained in this way to ensure that figures could be clearly interpreted. Cold Detection Threshold (CDT), Warm Detection Threshold (WDT), Thermal Sensory Limen (TSL), Paradoxical Heat Sensations (PHS), Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Mechanical Detection Threshold (MDT), Mechanical Pain Threshold (MPT), Mechanical Pain Sensation (MPS), Dynamic Mechanical Allodynia (DMA), Wind-Up Ratio (WUR), Vibration Detection Threshold (VDT) and Pressure Pain Threshold (PPT).

Overall, there were a greater number of *Z*-scores (see figure 7) that fell outside of the 95% confidence levels within the total sample than would be expected by chance (n = 48, allocated to 19 individuals). For a sample of this size, with 13 QST parameters, 95% confidence interval (CI) levels estimate that 15 values would lie outside the 95% CI level of The DFNS reference data. This variance is driven by the larger number of abnormal *Z*-scores in the ASD group (n = 32 allocated to all 13 individuals) compared to controls (n = 16 allocated to 6 individuals); who show typical numbers of outlying scores.

Intra-individually, 95% CI dictates that one *Z*-score in the 13 QST parameters would potentially be outside this level, which suggests that only 15 of our participants are showing atypical QST patterns (where the number of *Z*-scores outside the 95% CI >=2). A greater number of ASD individuals were found to have extreme scores compared to controls, and the range of these scores was wider in ASD individuals (2-5) compared to controls (2-3). However, the average number of these scores per participant, in those that showed this atypical pattern, was similar between the groups (see table 8 for descriptive statistics). Therefore, although a greater percentage of autistic individuals may show atypical patterns of pain response, when considering these altered responses, they may be within a range seen in a similar neurotypical group.

Table 8:

Number of participants with atypical QST patterns and the mean number of abnormal Z-scores of each participant

	ASD	**Controls**	**Total**
No. of participants	10	5	15
Abnormal *Z*-scores	2.9 ± SD 1.101	2.8 ± SD 1.366	2.867 ± SD 1.325
Range of abnormal *Z*-scores	2-5	2-3	2-5

Note. Total number of participants in each group showing abnormal values (where the number of abnormal values >=2; i.e., are outside the 95% CI of the reference data).
The number of abnormal values per individual in the groups is given as a mean ± *SD*, and range.

Furthermore, 1 autistic individual showed sensory distinctive features in the form of PHS; experiencing a warm, hot, or painfully hot sensation in response to the cold stimulation, that usually does not occur in healthy subjects and two felt allodynia to non-painful stimuli (DMA). These observations suggest that in this small population of autistic individuals that there are notable changes in peripheral function. Although these features do not appear to be typical of ASD, this does suggest sub-groups of ASD in which altered somatosensory processing may be present. Further, it appears that differences in sensory processing in some individuals may not simply be in terms of magnitude of response. Rather, it might reflect the presence of phenomena not typically seen in neurotypical individuals.

2B.4 Discussion

The current experiment investigated somatosensory perception in autistic individuals to test the hypothesis that the different pain behaviours observed in anecdotal accounts were the result of an alteration in somatosensory mechanisms. For this reason, and to allow the comparison to published norms, 13 autistic adults and 13 age- and gender- matched control participants without autism, underwent a standardised and normed QST protocol (DFNS: Rolke, Magerl, et al., 2006). No observable consistent pathological QST pattern suggesting a defined nerve fibre dysfunction, which could account for the altered pain behaviours observed, was found. The ASD group showed no systematic changes in their QST pattern.

Group differences were found, however, for both mechanical pain threshold (MPT; pinprick stimuli) and mechanical detection threshold (MDT; von Frey filaments), with the ASD group showing higher thresholds for both. Although the ASD group had higher thresholds compared to the control group, data for both groups reside within the normal distribution of healthy individuals, as established by The DFNS, indicating that although the ASD group may be less sensitive to mechanical pain than controls this sensitivity is not

clinically significant. However, ASD group mean value for MDT fell outside the normative range for healthy individuals, suggesting a clinically significant degree of sensory loss at the group level. Normal z scores for other clinically related QST parameters – such as vibration detection threshold – do suggest, however, typical Aβ-fibre function (Gröne et al., 2012).

Vibrotactile and punctate stimulation are both communicated via Aβ-fibres, though detected by different receptor pathways, which may account for the aforementioned differences. High frequency vibration is detected via rapidly adapting Pacinian corpuscle and generally have a large receptive field. Mechanical stimulation, on the other hand, are detected via slowly adapting Merkel cell-neurite complex receptors and is tactile detection via indentation depth (Delmas et al., 2011). Different Aβ-fibre phenotypic alterations may therefore be present and be stimuli specific, due to detection of such stimuli by their specific receptors. Such differences are highlighted in the evidence when contrary to the sensory loss of MDT measured by von Frey, increased sensitivity to vibration is reported (Cascio et al., 2008). There is greater difficulty in comparing vibration results in the literature, due to the varied vibration frequencies used (Blakemore et al., 2006; Güçlü et al., 2007), yielding very different results which may similarly be a result of different receptor activation (Lumpkin et al., 2010; McGlone et al., 2014; McGlone & Reilly, 2010). It must also be noted that the use of a tuning fork for vibrotactile assessment is sensitive enough to identify neuropathy – as intended – however, may not be sensitive enough to measure more subtle changes in threshold. Findings for MDT are in line with Fründt et al., (2017) who similarly report a significant loss of function for mechanical detection in ASD participants using the same standardised testing from the QST battery.

Similar to Fründt et al., (2017) who report PHS and DMA in two autistic individuals (see also Duerden et al., 2015), three participants showed distinctive sensory features in the

form of paradoxical heat sensations (*n* = 1; PHS) and dynamic mechanical allodynia (*n* = 2; DMA), that do not usually occur in healthy individuals or the control group on the upper limbs. Given that the different QST parameters did not reveal any specific signs of nerve fibre dysfunction in both studies, we concur with the author's suggestion that central mechanisms determine PHS in the ASD groups. Studies of patients with CNS demyelination confirm central processing issues that result in PHS (Hansen et al., 1996). Limited research has attempted to understand the central processing of pain in ASD using neuroimaging techniques. This research supports the idea that changes in pain processing in ASD is complex: suggesting that there is an initial processing which is similar to controls, however, there is a reduction in neural activity during sustained pain that is not present in controls (Failla et al., 2018). This gives further support to the need to be flexible about how pain experience is considered in ASD.

A further phenomenon observed by this experiment and that of Fründt et al., (2017) is that of DMA. Both studies are the first to experimentally measure DMA in ASD, observing this in a subset of the ASD groups. DMA is the experience of perceiving innocuous touch, such as gentle stroking, as aversive, a phenomenon described in ASD sensory over-responsivity literature (Baranek & Berkson, 1994; Green et al., 2016; Reynolds & Lane, 2008). Central sensitisation i.e., changes in signalling in the spinal cord (Campbell & Meyer, 2006), is commonly thought to underlie DMA (Gierthmühlen et al., 2012), as it is the increased response of neurons to stroking stimuli. Intriguingly, some groups have offered a peripheral explanation for DMA (Liljencrantz et al., 2013), whereby an alteration in C-tactile afferent function, which typically mediates a pleasant percept associated with low force slow stroking touch, communicates noxious experience. This explanation then lends weight to research suggesting that an early mechanism behind ASD may be an alteration in CT fibre function (Cascio et al., 2019; Gordon et al., 2013; Kaiser et al., 2016; Walker & McGlone,

2013). It is clear that this proposition requires further investigation. However, QST cannot fully distinguish between central and peripheral alterations (Mücke et al., 2014), therefore we can only speculate at this time.

The data also indicate either significant group differences, or sensory phenomena that do not occur in healthy individuals, in those tests which are reaction time-exclusive i.e., method of levels. In these tests reaction time is minimised because participants are generally responding to whether the stimulus is perceived as painful, which in turn can determine the next stimulus that is presented. In contrast, findings from tests which utilised the method of limits approach, such as the thermal tests, showed no group differences (Siao Tick Chong & Cros, 2004). It is well known that the method of limits approach is reaction time inclusive (Lynam et al., 2006; Siao Tick Chong & Cros, 2004) and that reaction time has significant influence on detection thresholds (Huang et al., 2010; Saville et al., 2012; van den Bosch et al., 2017). Furthermore, several studies have shown that reaction times are slower in autistic individuals (Baisch et al., 2017; Herrero et al., 2000; Inui & Kakigi, 2012). Taken together this suggests that threshold values are elevated in ASD, represented in the data as non-significant results. In order to address this, recent research suggests using reaction time exclusive methods (Treutwein, 1995; Watson, 2017; Williams et al., 2019), however, this approach would still not fully address whether reaction times influence threshold estimates across a range of sensory modalities in ASD. It would be pertinent to include a measure of reaction time in future research, with the acknowledgement that reaction time as the onset of movement, such as pressing a button is only an estimate of the delays that are incorporated in the underlying process (e.g., sensory activation, conduction times, synaptic delay and time to generate force; Cavanagh & Komi, (1979); Letz & Gerr, (1994)). Rather than including reactions times as a covariate, it may be best to include it in a moderation analysis, such that

it allows for an interaction which indicates the magnitude of a group difference dependent on the level of the covariate (Leppink, 2018).

There are striking similarities between our findings and those of (Fründt et al., 2017). Both were independently conducted, in parallel, and sought to use The DFNS QST protocol to identify differences that might exists in somatosensory function is ASD. Both studies found little evidence for a diagnosis-wide change in either somatosensory detection or pain thresholds. Both also found that when *Z*-scores were compared to published norms that more autistic individuals showed atypical data points, suggesting that individual differences may be of importance. This replication is particularly powerful as psychological sciences wrestle with the reproducibility crisis (Aarts et al., 2015). Here, independent verification of findings has been achieved, to provide a platform upon which to build future research.

An advantage of the standardised QST method is the published normative data which provides clear definitions of sensory loss and gain. The ASD phenotype can drastically differ and has large individual differences meaning the typical group analyses may not be advantageous to understanding this spectrum condition. Such published norms, which an individual's QST pattern can be compared to, provides the opportunity to quantify individual cases. Individual analyses revealed a greater inter-individual variance with more *Z*-scores outside the 95% confidence interval of The DFNS published normative values in the ASD group (n = 32). This variance was present in all QST parameters and was not driven by a single participant (n = 13 participants). This might reflect the general heterogeneity of the ASD group; such heterogeneity belies the attempt to group this population under one diagnostic umbrella. The utility of this type of analysis is best shown in figure 3, which illustrates the sensory profiles of autistic individuals, and their sensory changes (see results

section 2B.3.4). This also allows individual differences in the phenotypic presentation of ASD to be considered alongside their QST pattern.

The approach provides some insight into variation across domains, known as dispersion. However, there were still large standard deviations suggesting intra-individual variability within single participants across trials (Costa et al., 2019). Data elsewhere has shown intra-individual variability as more substantial in autistic individuals, supporting our data (Geurts et al., 2008). The fact that ASD is not a homogenous group is additionally supported by these data. Such variability, could impact on the accuracy of mean group threshold values, and so future research should consider variability both within the design and analysis. The simplest way is to calculate individual standard deviations or to calculate residualized standard deviations, which provide control for systematic between- and within-subject confounds in the raw scores, therefore generating greater accuracy (Stawski et al., 2019). However, to calculate such, more trails would be needed than were utilised here. In a recent paper, Williams et al., (2019) investigated the role of intra-individual variability in thermal perceptual thresholds. Gini's Mean Difference (GMD) scores (measure of variability) predicted higher detection threshold estimates, and GMD outliers had substantially higher thresholds. These results indicate that increased variability between trials systematically biases threshold estimates away from the starting temperature. Considering that both inter-individual variability and reaction times have been found to bias the data, inflating thresholds, results from our study that indicate no group differences, should be interpreted with caution. However, despite intra-individual variability inflating perceptual thresholds, Williams et al., (2019) report similar findings in that autistic individuals did not differ in thermal detection thresholds compared to controls. Despite this, it may be prudent to control for these factors by including these as potential interaction factors in future analysis.

Following from the previous suggestion of using moderation using reaction times as an interaction, it may also be pertinent to include variability within this too.

In order to gain a self-report measure of motivation for pain avoidance, individuals were asked: "how much would they like to avoid feeling the stimulus again?". However, these results were inconclusive. Self-report measures of pain motivation do not appear therefore, to access motivation in a way that provides a clearer or deeper understanding. For this reason, elegant experimental paradigms that have been used in healthy populations for understanding goal attenuation of avoidance behaviour could be adopted and utilised in an ASD population (Claes et al., 2014a, 2015; Meulders & Vlaeyen, 2012, 2013). Such experiments can implicitly test motivation that goes beyond conscious self-reporting by measuring behavioural responses and understanding avoidance in the context of multiple goals. This could be of vital importance in a population driven to achieve their repetitive or restrictive behaviour patterns regardless of other incoming behaviourally motivational stimuli, such as pain. Furthermore, given that the QST battery revealed typical nerve fibre function and that CPM appeared typical, this approach may help to pull apart the altered pain behaviours by considering top-down modulation of pain.

Given the nature of sensory testing- applying a stimulus and recording verbally the perception of that stimulus, the underlying mechanisms can only be judiciously speculated upon. The pain experience in such studies is delivered in controlled environments, devoid of motivational context or other environmental cues. This absence of environmental context, results in a lack of knowledge about how distraction and other psychological effects might affect pain perception in ASD or how they modulate the simpler sensory experience of an input. It is also understandable, brief and cutaneous in nature, which may not reflect the diversity of pain in the real world (the relative merits and challenges of QST measures have

been considered extensively elsewhere e.g., Backonja et al., (2013); Maier et al., (2010). By comparison, naturally occurring pain is frequently endogenous, of longer duration, can be diffuse, and typically involves multiple pain systems. Further, ethical standards of pain induction that mitigate the threat of pain, fundamentally altering the emotional and motivational significance of pain is arguably a key feature of pain that emerges naturally (Edens & Gil, 1995). The cost of such control is the potential lack of relevance to naturally occurring pain (Robertson & Low, 2006; Rollman, 2005). The methodological challenge is to develop techniques that combine the benefits of laboratory control with the relevance of pain that emerges naturally (Moore et al., 2013).

The findings of the present experiment should be considered in light of several limitations; notably the small sample size, which is common in the literature (Cascio et al., 2008; Duerden et al., 2015; Fründt et al., 2017; Güçlü et al., 2007). Many autistic individuals find novel environments distressing and therefore may be unlikely to participate. Additionally, fear of pain and anxiety may likely reduce participation in experimental pain research (Karos, Alleva, et al., 2018). This paired with an exclusion of those with anxiety and depression, placed further limitations on recruitment numbers. This exclusion could be disadvantageous, not only because it resulted in a smaller sample size, but also because it could limit the ecological validity of the study. Analysing ASD as a single group, without these comorbidities may blur different aetiologies responsible for this heterogenous group, not only because co-morbidity tends to be the rule not the exception in ASD (Deliens et al., 2015; Hollocks et al., 2019; Rosen et al., 2018; Thompson et al., 2016), but also that these differ in their trajectories (Doshi-Velez et al., 2014). Levels of co-morbidity have also shown to provide clues to the aetiology, and pathophysiology of both the index and co-morbid condition as common patterns of influences or vulnerabilities cluster in an individual (Dell'osso & Pini, 2012; Klein & Riso, 1993; Valderas et al., 2009). This control, however,

gives added validity to the results, as these conditions are known to have effects on pain perception (for review see Goesling et al., (2013); Thompson et al., (2016)). Future studies should adopt this singular diagnosis approach and increase sample size, regardless of the difficulties caused by frequent psychiatric comorbidities in this population (Joshi et al., 2013).

A related limitation is the inability to examine the effect of individual differences on pain responses, specifically IQ. Although participants had been formally assessed for a diagnosis of ASD and had been assessed for IQ in the normal range by a trained clinician, it was not possible to obtain detailed psychometrics. Further independent testing of IQ within the experiment, was deemed to be burdensome and in the interests of the well-being of the participant was excluded from the protocol. The addition of an IQ test to an already extensive protocol may have increased stress and therefore resulted in an unrepresentative response to stimuli. It would be beneficial in future studies to find mechanisms to understand key individual differences which might affect pain response in ASD. IQ in particular may be an important factor to consider as it has been shown that thermal pain response may be correlated with IQ, with participants with a lower IQ score having higher thresholds (Duerden et al., 2015). It was not possible to test this finding in the current research.

In conclusion, there was no systematic alteration to suggest an underlying dysfunction in the cutaneous somatosensory modalities tested in this experiment. There was a larger number of outlying *Z*-score values within the ASD group. Further, dynamic mechanical allodynia and paradoxical heat sensations were present in some ASD participants, which is typically only observed in patients with peripheral neuropathy. Central processing and integration of sensory information rather than peripheral perception seems to be a better candidate for further research within ASD. In order to test this theory, future studies should

focus on combining QST measurements with neuroimaging to detect probable processing differences. Additionally, studies could use experimental paradigms that test pain motivation to assess top-down modulation as a potential cause of altered pain behaviours in this population.

Chapter 3. Attenuation of Pain Avoidance Behaviour by a Competing Goal

Chapter 3. Introduction

The previous Chapter investigated detection and pain thresholds using QST battery. Results indicated individual differences in the processing of nociceptive stimuli, but not global systematic population level changes in pain perception (Fründt et al., 2017; Vaughan et al., 2019), therefore changes in pain response in ASD cannot be explained by a simple perception-action model. That is to say that pain perception, resulting in the behaviours described in the anecdotal accounts, are not fully explained by peripheral nociceptive stimuli evoking a response. The experience of a potentially noxious input, as one which we might call "pain", is more complex than this simple feedforward process (Apkarian, Bushnell, & Schweinhardt, 2013), including the motivational state and the goals and intentions of future actions (Eccleston & Crombez, 1999; Fields, 2004; Ossipov et al., 2010; Price et al., 1999; Tracey, 2010; Villemure & Bushnell, 2002). Additionally, expectation and belief are important contributors. Expectation of pain generally biases perception in the direction of that expectation, wherein expecting pain to be more intense results in people reporting lower pain thresholds (Benedetti et al., 2007; Benedetti et al., 2003; Voudouris et al., 1989). Pain avoidance is, therefore, motivated by the perceived threat of pain arising from expectancies about pain, even erroneous expectancies (Peerdeman et al., 2016). Additionally, this process is also reliant on the type and intensity of the painful stimulus. Pain of a sufficiently high intensity will therefore result in a learning process whereby an individual will reduce or even stop behaviours associated with a painful outcome (Boston & Sharpe, 2005; Schoth et al., 2014). Evidence points to a number of distinct motivational systems of action, including innate and goal directed systems (Vlaeyen et al., 2016).

Since pain is motivationally relevant, it can predict performance of particular behaviours (Legrain et al., 2012; Peters, 2015), drawing on cognitive resources that interfere

with other tasks (Crombez et al., 1994) in order to promote these behaviours, for example a focus on withdrawal reflex. In ASD, there is a high saliency towards achieving restrictive repetitive behaviour patterns (RRBs: Cascio et al., (2014); Uddin et al., (2013)) with a strong focus on performing tasks. Specifically, this symptom or behaviour means that individuals have a narrowness of focus and a cognitive inflexibility in terms of an insistence towards repetition and rhythmic response (Leekam et al., 2011). Additionally, research frequently shows an association between sensory processing abnormalities and RRBs (Chen et al., 2009; Wigham et al., 2015). Findings indicate a particular relationship with tactile, visual and auditory hyper-responsiveness and increased RRB's (Chen et al., 2009). However, this research fails to consider a causation for this and fails to consider that RRBs are fundamentally a motivation, influencing behaviour, in order to maintain a homeostasis of their environment (Leekam et al., 2011)

Pain motivation is the mechanism by which imminent harm is terminated and future harm minimized, i.e., approach or avoidance behaviours. The motivational value of a nociceptive stimuli is therefore a key component of pain perception, incorporating not only the stimuli but the predication of pain (Van Damme et al., 2010). The perception of pain includes pain unpleasantness, which incorporates the overall motivational significance of nociceptive stimuli, and pain intensity, which differs from unpleasantness in that it is thought to be the accurate representation of pain (Seymour & Dolan, 2013). Therefore, in its simplest action system, pain is typically and simply wired to draw attention and interrupt other processes or goals. It might be expected that this would interrupt even the restrictive repetitive behaviour patterns discussed above. This is an important process that is dependent on the interaction between pain-related characteristics and other ongoing processes whereby pain-goals become the priority and other information is inhibited - in order to elicit the aforementioned protective responses.

Recent revision to the Fear Avoidance models of pain have integrated a motivational approach and considers that this pain-related goal is one of multiple demands or goals occurring simultaneously, sometimes competing with these other goals (Botvinick & Braver, 2015; Crombez, Eccleston, Van Damme, et al., 2012; Van Damme et al., 2008). In this context of multiple goals, the pursuit of one goal may interfere with another, even one as interruptive as pain, giving rise to goal conflicts (Boudreaux & Ozer, 2013). Research using this approach has shown that a valued reward can attenuate pain avoidance behaviours (Claes et al., 2014, 2015, 2016; Van Damme et al., 2012). This is regardless of pain-related fear or typical *Fear Avoidance,* as participants are more hesitant in performing a painful movement than a safety movement when there is no valued reward (Claes et al., 2014a, 2015). Furthermore, goal conflicts that produce negative affect are related to pain-related fear, when the goals are between negative competing goals (Schrooten et al., 2014). It, therefore, postulates that those who have other goals with a higher saliency than pain avoidance may be more inclined to expose themselves to pain.

In terms of ASD, despite sensory deficits being considered from a position of distress and harm, there is a lack of consideration of pain itself, particularly of multiple goals and a motivational fear avoidance model of pain within the research. In the previous context of conflicting goals, and in performing a rewarded or otherwise important goal, autistic individuals may show reduced responsiveness to a, for example, painful cue, therefore showing a reduction in learned pain avoidance, such as those reported in the anecdotal accounts. Currently, this consideration in terms of an explanation for the pain behaviours mentioned in anecdotal accounts requires investigation, specifically for a lack of pain response in autism. This project, therefore, utilises a volitional joystick task (VJT; Claes et al., 2014), in order to investigate the proposed behaviours in terms of a motivational model of pain. The VJT is a paradigm which exemplifies a typical human fear conditioning

experiment where arm movements performed with a joystick are followed by a painful unconditioned stimulus, which becomes a threat signal after several pairings and thus elicits a fear response (Meulders et al., 2011; Meulders & Vlaeyen, 2012). In a differential paradigm, a control stimulus is included that is never followed by pain and is thus a safety signal (Domjan, 2017). The addition of a competing goal then allows the measurement of pain attenuation behaviours, capturing motivational components. Understanding this system is the critical next step to understanding pain in ASD considering earlier findings, namely no group level differences in response to peripheral stimuli (see Chapter 2) as well as the described insensitivity in the anecdotal evidence. It is hypothesised that, pain avoidance behaviours will be attenuated to a larger extent in the ASD group, compared to controls, due to a greater motivation by a valued reward, since an ASD characteristic is a high saliency towards achieving restrictive repetitive behaviour patterns. the attenuation of pain avoidance behaviours by a valued reward will be greater in the ASD group.

3.2. Methods

3.2.1 Sample Size Calculation

Selecting an appropriate sample size to capture within-person change for mixed repeated measures designs can be complicated, since measurements taken from the same participant are correlated and these correlations must be accounted for in calculating the appropriate size (Guo et al., 2013). Some current software packages oversimplify the assumptions about this correlation pattern and as such, several approaches have become available to address this limitation, although many of these are reliant on greater statistical knowledge and skills, for example advanced modelling abilities (D'Amico et al., 2001; Miles, 2003). One alternative is to estimate power as if the measures were independent, in this case, group differences between the within-subjects factors. However, this approach does not

account for the greater power repeated measures designs have since they capture within participant change and reduce variability (Lakens, 2013). Therefore, presented below are two sets of calculations, both using G*Power, one utilising *a priori* sample size calculation for mixed ANOVA in full i.e., 2*2*2 design, and the second using independent *a priori* tests. In the case of the *F*-test *a priori* calculation sample size is suggested as 16, in the case of independent *a priori* tests the calculation suggests 66 (for a 2* (group) 2(within-subjects factor)).

Table 9:

*A priori Sample Size Calculations of F-tests with G*Power.*

		ANOVA: Repeated measures, within-between interaction	**ANOVA: Repeated measures, between factors**
Input:	Effect size f	= 0.4034733	= 0.3937008
	α err prob	= 0.05	= 0.05
	Power (1-β err prob)	= 0.95	= 0.95
	Number of groups	= 2	= 2
	Number of measurements	= 4	= 2
	Corr among rep measures	= 0.5	= 0.5
	Nonsphericity correction ε	= 1	-
Output:	Noncentrality parameter λ	= 20.8372101	= 13.6400282
	Critical F	= 2.8270487	= 3.9909238
	Numerator df	= 3.0000000	= 1.0000000
	Denominator df	= 42.0000000	= 64.0000000
	Total sample size	**= 16**	**= 66**
	Actual power	= 0.9676625	= 0.9532590

3.2.2 Participants

Sixteen adults (14 males) who had not previously undergone a pain-related experiment with us, aged between 18 and 59 years were recruited (*M* = 25.13, *SD* = 12.23). Eight ASD participants (7 males and 1 female) with a mean age of 24.38 years (*SD* = 4.13) were recruited via the university's participant panel, had a diagnosis from a specialist diagnostic service within a local hospital trust and had received their diagnosis based on the DISCO and/or ADOS from a trained clinician. Diagnosis letters were obtained from participants where possible, which confirmed diagnosis and IQ values >70. Additionally,

educational level was taken as a proxy measure. Those suffering from chronic pain, diabetes, Raynaud's syndrome, eczema, or sensitive/broken skin were excluded, as were those with a reported history of a severe psychiatric disorder or learning disability.

Eight participants without an autism diagnosis were recruited through advertisement, selected to match each autistic individual on age: within a limit of ±5 years (M = 25.88, SD = 4.78) and gender (7 males). All were subject to the same exclusion/inclusion criteria mentioned, with the addition of SIB i.e., self-cutting to the exclusion criteria. This was only applied to the individuals without ASD because for autistic individuals, SIB tends to be classified as "stereotyped SIB" as opposed to the "impulsive SIB" that is habitual in nature and generally observed in individuals with a serious psychiatric illness (e.g., self-mutilation) or typically developing adolescents and adults (e.g., self-cutting; Minshawi at al., (2014); Yates, (2004)). Furthermore, the nature of SIB in autism may be a behaviour of interest, therefore a comparison to individuals without SIB, especially an SIB that is phenotypically and psychiatrically different, is essential. Although they were not explicitly matched on IQ, the control group were from the general population, suggesting IQ>70 and educational level taken as a proxy measure for IQ. All participants in both groups were without pain medication or alcohol at least 24 hours before the investigation.

As groups (n = 8 per group) were age and gender matched they did not significantly differ; $t(11) = .554$, $p = .590$ and $\chi^2(1) = 0$, $p = .767$, respectively. As expected groups had significantly different AQ scores $t(11) = .4.780$, $p = .001$, with the autism group showing greater autism trait severity (see table 9).

Table 10:

Characteristics and questionnaire results of ASD and Control group

Characteristic		ASD	Controls	Total
No. of participants		8	8	16
No. of participants with:	ASD	3	-	3
	Asperger's	5	-	5
Age		24.38 (4.13)	25.88 (4.78)	25.13 (12.23)
Gender Female		1	1	2
Male		7	7	14
Autism Quotient (AQ)*		34.50 (.752)	16.25 (2.09)	25.38 (11.09)

Note: All values are given as mean (SD). *p<.05. ASD (Autism Spectrum Disorder).

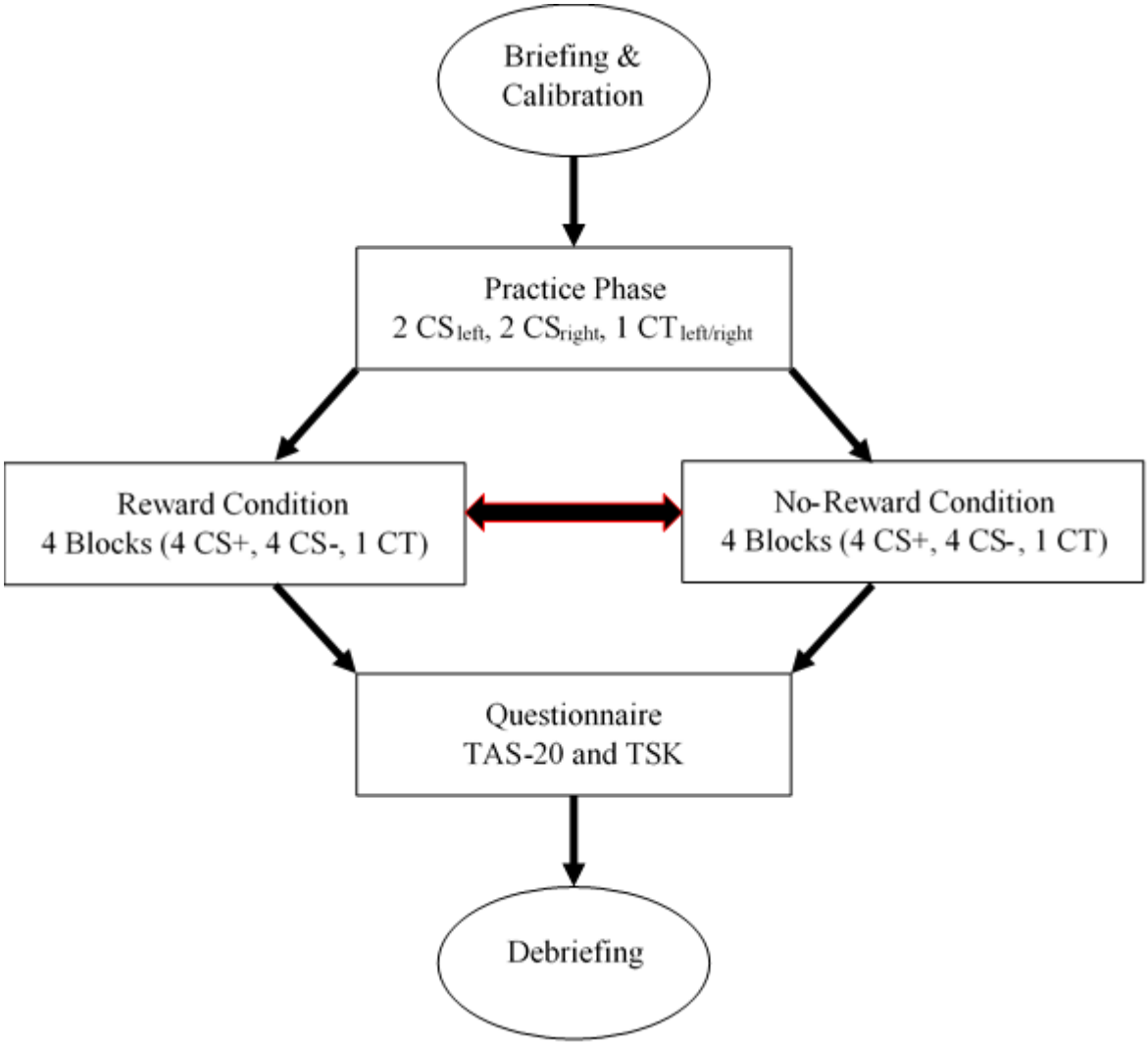
The experiment was approved by Liverpool John Moores Ethics Committee (REC ref: 15/NSP/054). Prior to consent participants received information both orally and in writing that painful stimuli would be administered, but that the intensity of the stimulus would not exceed their individual tolerance and that it was what is considered in pain administration as instantaneous i.e., exceptionally brief lasting only 300mS.

3.2.3 Procedure

All participants gave informed consent after being briefed and completed the health screening including the AQ, Repetitive Behaviour Scale-Revised (RBS-R), PCS, and Fear of Pain (FP) online prior to attending the laboratory for the experiment. The experiment included determination of thermal pain and tolerance levels and a volitional joystick task. The task included a calibration phase, a practice phase, and an experimental phase, consisting of a reward and no-reward condition. It lasted approximately 75 minutes. A graphical overview can be seen in figure 8.

Figure 8.

Graphical overview of experimental design and procedure showing all phases of the experiment from briefing to debriefing, including the number of blocks (n = 4) and movements (n = 9) in each condition (Reward and No-Reward) of the volitional joystick task



Note. In the practice phase CS_{left} is a movement signalling to move left, and CS_{right} signals a right movement, whilst $CT_{left/right}$ was the opportunity for participants to learn the cue for being able to choose which direction to move i.e., two signals of the same colour appeared. Experimental design. CS+ indicates movements that are followed by either both the pain-US and the reward-US (Reward condition) or by the pain-US (No-reward condition) in 50% of the trials. The actual movement (left/right/up/down) that acted as the CS+ were counterbalanced in conditions, and across participants. CS- indicates a safety movement: that is one that is never followed by a US. CT indicates the choice trials, where participants were free to choose which direction the moved. These always occurred at the end of each block and when choosing a CS+ movement it was always followed by both US's 100% of the time. Movements were conducted in either vertical or horizontal planes and were counterbalanced across conditions for example: Up = CS+ in the reward condition, therefore the CS- was down (horizontal plane), therefore the no-reward condition was in the vertical plane where CS+ = left and CS- = right. Conditions were counterbalanced across participants within each group (indicated by the red outlined arrow). TAS-20 is The Toronto Alexithymia Scale and the TSK is The Tampa Scale for Kinesiophobia.

3.2.4 Materials

3.2.4.1 Questionnaires

All questionnaires were completed by both groups. The AQ was used to quantify autistic trait severity, meanwhile the RBS-R and The Toronto Alexithymia Scale (TAS-20) were used to measure symptomology associated with ASD. The PCS and FP to gain a measure of pain catastrophizing and fear of pain, for descriptive purposes. An additional scale was used to measure Kinesiophobia; The Tampa Scale (TSK). Both the AQ and the PCS are described in Chapter 2 (see section 2A.2.2.1.1 and 2A.2.2.1.2).

3.2.4.1.1 Fear of Pain Questionnaire-III

Assesses the fear of pain using 30 items, each rated on a 5-point Likert Scale from 1 (Not at all afraid) to 5 (Extremely afraid), with a maximum score of 150. Participants were asked to consider how fearful they were of experiencing the pain associated with each item. Pain examples are divided into three subscales: Severe pain, Minor pain, and Medical pain. Studies have supported the validity and reliability of the scale (McNeil & Rainwater, 1998; Osman et al., 2002).

3.2.4.1.2 Repetitive Behaviour Scale – Revised

Consisting of 44 items, the RBS-R measures the breadth of repetitive behaviour. It covers the full spectrum of suspected repetitive behaviours grouped into subscales, including: Stereotyped Behaviour, SIB, Compulsive Behaviour, Routine Behaviour, Sameness Behaviour and Restricted Behaviour (those which do not overlap in content to the other behaviour types listed). Each behaviour type is rated on a 4-point Likert Scale of how often said behaviour occurs (0: Does not occur to 3: Occurs and is a severe problem). Lastly participants are asked to consider all of the behaviours described and provide a global rating

for how much these impact functioning using a numeric rating scale 0-100 (0: not a problem to 100: as bad a problem as you can imagine). Studies have supported the validity and reliability of the scale for use in ASD studies (Lam & Aman, 2007; Martínez-González & Piqueras, 2018).

3.2.4.1.3 The Toronto Alexithymia Scale

Alexithymia is described as a subclinical phenomenon marked by difficulties in identifying and describing feelings and difficulties in distinguishing feelings from the bodily sensations of emotional arousal (Nemiah et al., 1976). This scale is a 20-item instrument that is most commonly used to measure this phenomenon. Each item is rated between 1 (strongly disagree) and 5 (strongly agree), with items grouped into subscales of difficulty describing feelings, difficulty identifying feelings and externally oriented thinking. A score greater than 61 is equal to alexithymia and a score between 52 to 60 represents possible alexithymia. The scale is both commonly used, with validity and reliability supported in several studies (Bagby et al., 1994; Parker et al., 2003).

3.2.4.1.4 The Tampa Scale for Kinesiophobia

In order to account for a fear of physical movement, particularly a movement related to experiencing pain, such as moving a joystick that is sometimes paired with a painful stimulus, a measure of Kinesiophobia was included. This would allow us to have confidence that results were reported were not due to Kinesiophobia - a fear of physical movement and activity resulting from a feeling of vulnerability due to experiencing pain (Larsson et al., 2016). The Tampa scale of Kinesiophobia measures the subjective fear of movement, discriminating between non-excessive fear and phobia using 17 items scored on a 4-point Likert scale, with a maximum score of 68. Any score over 37 is considered to represent a high score and therefore a likelihood of a feeling of vulnerability to pain/injury from

movement. The scale has been previously validated by (H. Huang et al., 2019; Swinkels-Meewisse et al., 2003).

3.2.4.2 Determination of Heat Pain Threshold and Tolerance

Prior to the Volitional Joystick Task, heat pain threshold (HPT) was measured using the standard procedure described in Chapter 2, section 2A.2.2.2.1. Alongside this a measure of heat pain tolerance (HTOL) were also obtained. In brief this followed a similar protocol to the HPT; a thermode was heated at 1°C/second until participants pressed a button to indicate they had reached a point at which the painful temperature could no longer be tolerated. This was to ensure there were no differences in peripheral temperature processing that may account for differences in outcomes of the experiment.

3.2.4.3 Volitional Joystick Task Stimuli

3.2.4.3.1 Thermal Stimulus

A thermal CHEPS stimulus acted as painful unconditioned stimulus (pain-US). The pain-US is delivered by a Medoc Pathway Advanced Thermal Stimulator. A CHEPS thermode, attached to the dominant forearm, was heated from a baseline temperature of 32°C, at a ramp rate of 70°C/second until the thermode reached 52°C, at which point it then returned to baseline at 40°C/second. The stimulation lasted 300 milliseconds.

3.2.4.3.2 Reward Stimulus

A digital lottery ticket representing the chance to win an extra £20 voucher acted as the conditioned stimulus (reward-US) and was introduced during the reward condition.

3.2.4.3.3 Conditioned and Control Stimulus

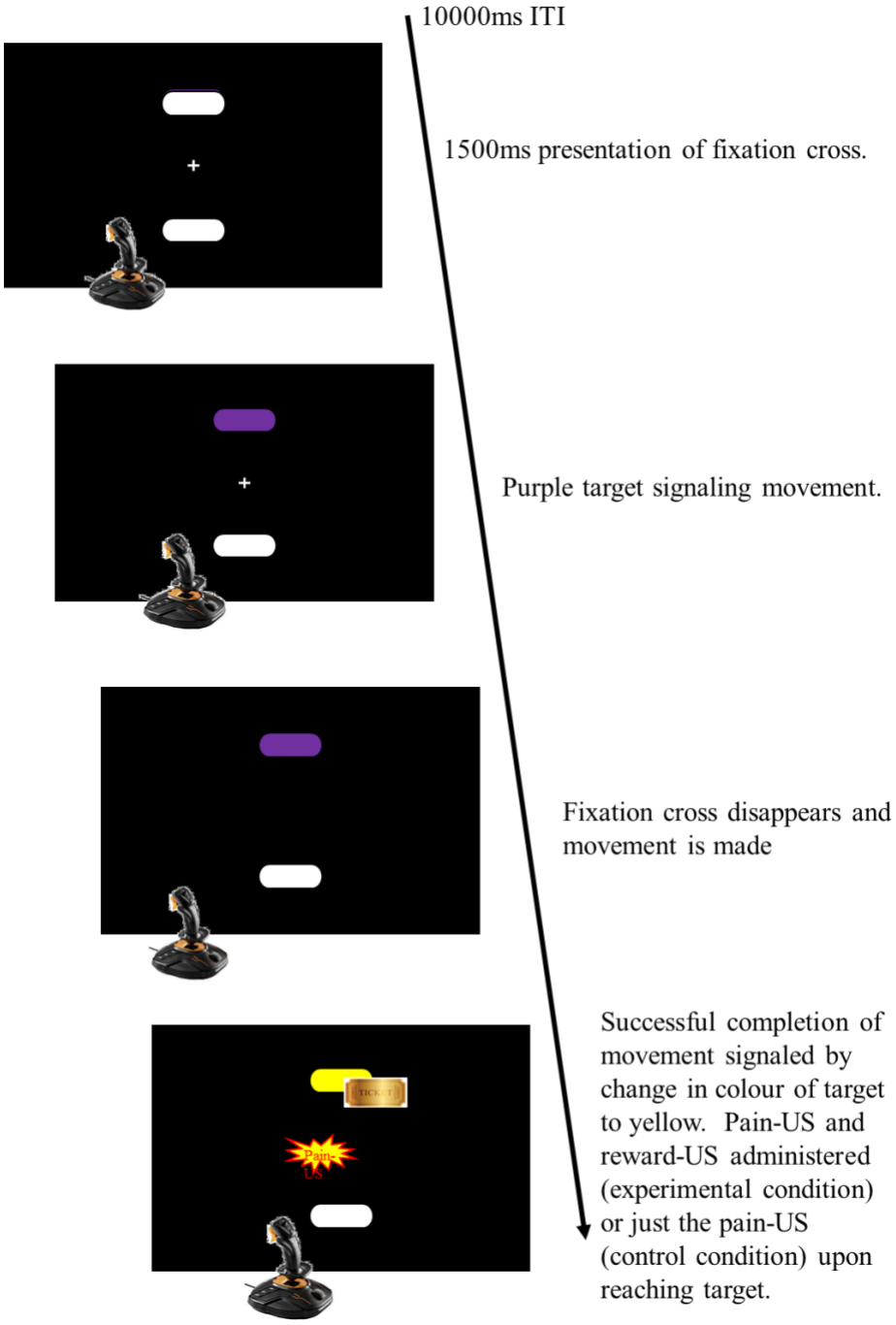
The pain-US was delivered after completion of a movement in one direction (CS+) but not in another (CS-). The CS+ during the reward condition included the pain-US and the reward-US.

3.2.4.4 Volitional Joystick Task

The task involved participants moving a joystick towards a signalled target. They were presented with a fixation cross and two white boxes that acted as the target. The movement to be performed was signalled by a change in colour from white to purple of the corresponding target, this acted as the signalled target. Upon completion of the movement the purple box changed to yellow. Some of the movements were followed by the pain-US, some followed by the pain- and reward-US and some were safe, dependent on the phase and the condition. Figure 9 presents a graphical overview as an example.

Figure 9.

Graphical overview of a trial within the volitional joystick task. This represents a trial in which the reward-US was paired with the pain-US.



Note. Shows an example of the overall trial timings and process for a vertical trial, horizontal trials will be identical in presentation, but movements made left/right. A purple target signalled which direction to move towards. A correct movement is signalled by the target changing in colour from purple to yellow. During the reward condition, when the CS+ was reinforced with the reward-US a golden ticket image appeared. Pain-US was administered as soon as the target was reached. During the choice trials presentation was the same when a participant chose a CS+ movement, when a CS- movement was made, both targets appeared yellow.

3.2.4.4.1 Calibration Phase

During this phase, participants experienced the thermal stimulus that would act as the pain-US for the task, in order to obtain an individual endurance level. Participants were sat in a chair approximately 0.6m away from the computer screen. They were asked to rate their ability to endure the stimulus using a 0 to 10 numeric rating scale (NRS; 0 completely able to endure to 10 meaning completely unable to endure). If a participant rated endurance at 10 on the NRS, a lower maximum temperature was implemented, and the procedure repeated until an endurance level less than 10 was achieved. *T*-rests revealed that the ASD group (M = 4.38, SD = 2.77) did not significantly differ from controls (M = 2.06, SD = 2.34) in their ability to endure the pain stimulus $t(14) = 2.312$, $p = .093$. Participants were then asked having experienced the painful stimulus, did they consent to continuing with the experiment and to repeatedly receiving this stimulus at their individual endurance level. Intensity and unpleasantness ratings of the stimulus were then obtained using the same NRS (0 meaning no pain, 10 meaning most intense/unpleasant pain imaginable).

3.2.4.4.2 Practice Phase

This phase allowed participants to familiarize themselves with the experimental task and how to operate the joystick. They were instructed to move the joystick as fast and as accurately as possible towards the signalled target as soon as the fixation cross disappeared and were instructed at every stage about what was the target (white box), when they were being signalled to move (purple box) and that if they achieved a successful movement the box would change colour again (to yellow). During this phase, neither the pain-US nor the reward-US was presented. Participants could monitor their own joystick movements via a cursor shown on the screen. When a non-signalled movement was performed, or the joystick left the starting region an error message was displayed (an error cross).

Two blocks of five trials were run. The first block consisted of two horizontal movements (left/right), followed by one choice trial, i.e., participants had to choose which direction to perform. The second block was identical, only movements were made in the vertical plane (i.e., up/down). Each trial started with a 1.5 second presentation of the fixation cross and ended when the target was reached. The next trial started 10 seconds later.

3.2.4.4.3 Experimental Phase

A mixed design was employed wherein all participants in each group completed both the reward and no-reward conditions. The order that these conditions were completed were counterbalanced as were the movements to be made in each condition. Participants were randomly allocated to either completing the reward or no-reward condition first. They also manipulated the joystick in the horizontal plane (left/right) during the reward condition and in the vertical plane (up/down) in the no-reward condition or vice versa. The movement which acted as CS+ (paired with pain-US and reward-US) was also counterbalanced across participants, so that each movement acted as CS+ depending on the previous counterbalances.

At the start of each condition, the instruction to focus on the fixation cross was given as well as to perform the signalled movements as quickly and as accurately as possible, as soon as the fixation cross disappeared. At the end of the experiment i.e., after completing all phases, participants were also asked; “How important was it to avoid the thermal pain stimulus?” and “How important was it to earn the reward?” using a Likert scale ranging 0 (not at all important) to 10 (very important).

3.2.4.4.3.1 Reward Condition

In the reward condition a movement in one direction was followed by the pain-US and a reward -US (CS+), whereas movement in the opposite direction was not (CS-). On

some trials participants were requested to perform the signalled movement, whereas on others they could choose which direction to move.

There were four reward acquisition blocks consisting of eight trials (4*CS+ and 4*CS-). CS+ movements were immediately followed by the pain-US and the reward-US in half of the trails (50% reinforcement rate), whereas the CS- was never reinforced. All participants therefore received eight pain- and reward-USs in total during this condition.

Each block was followed by a choice trial in which participants could choose the direction they wished to move in. In these trials, CS+ was always followed by both US's (100% reinforcement rate), whereas CS- was never followed by either. If participants chose to move towards CS+, participants received both pain-US and reward-US (volitional part of the task).

At the end of each block, participants rated the pain intensity, unpleasantness and endurance of the pain stimulus.

Once during each block, before the start of one CS+ and one CS- movement pain related fear and pain expectancy were measured, using the following questions:

- "To which extent were you afraid that performing [left/right/up/down] movement was going to be painful?"
- "How likely were you to receive pain when the following movements were made; left/right, up/down"?

All were answered using a 10-point Likert scale.

3.2.4.4.3.2 No-reward Condition

The no-reward condition was identical to the reward condition, with the exception that the CS+ movement was only ever followed by the pain-US and not the reward-US (See figure 8 for overall view of trial).

3.2.4.5 Task Self-Report Measures

3.2.4.5.1 Outcome Measures

The primary goal of this experiment was to investigate the effect of pain on motivation to perform cued actions and whether a concurrent reward was able to attenuate pain-related fear. Participants were therefore asked to indicate to what extent they were fearful that the movement would be painful (pain-related fear) prior to performing that movement. Secondly, in order to determine if the reward-US had any effect on intensity, unpleasantness or endurance participants were asked to retrospectively rate to what extent the stimulus was painful, unpleasant and tolerable, using a 10-point NRS (0; not at all to 10; very much). Lastly, in order to determine if contingency learning occurred participants reported online, using a 10-point NRS, prior to a CS+ and CS- movement to what extent they expected the pain-US to occur (pain expectancy). All of these were considered in terms of whether the ASD group differed from the control group.

3.2.4.5.2 Additional Measures

To explore the role of goal importance on avoidance behaviour, participants indicated retrospectively how important they found the goal during the experiment using a Likert scale ranging 0 (not at all important) to 10 (very important). The questions were as follows: “How important was it to avoid the pain stimulus?” (pain-avoidance), and, “How important was it to earn the reward?” (approach-reward).

3.2.4.6 Task Behavioural Measures

3.2.4.6.1 Latencies

3.2.4.6.1.1 Initial Response Latency

Initial response latency was recorded for every movement and is considered as a proxy of the initial reaction or reflex response. It was defined in this experiment as the time from the disappearance of the fixation cross until participants left the start region. In order to capture this reflex response the invisible area around the fixation cross was set at 20 pixels, smaller than that of the response latency, which was replicated from Claes et al., (2014).

3.2.4.6.1.2 Response Latency

Response latency was recorded for every movement in order to give a proxy measure of avoidance behaviours. Response latency is defined in this experiment as the time from the disappearance of the fixation cross until participants left the start region; a very small invisible area round the fixation cross in the middle of the screen of 50 pixels (screen resolution of 1024*1280).

3.2.4.6.1.3 Response Time

Response time was recorded for every movement, defined in this experiment as the time from the disappearance of the fixation cross until participants reached either the signalled or chosen target as a measure of task completion.

3.2.4.6.2 Decision-making Behaviour

As a proxy measure of approach/avoidance decision-making behaviour, participants completed four choice trails per condition in which they could choose between a CS+ movement (pain-US and reward-US) or a CS- movement (safety movement; no pain-US).

3.2.4.7 Task Apparatus

The experiment was run on a Windows computer with an IntelCore2 Duo processor and 256 MB of video random-access memory. The experiment was programmed in E-prime Pro2 (Psychology Software Tools version 2.0) with a joystick (ThrustMaster VG, T1.6000M FCS) used for performing the movements, i.e., towards left, right, up, down. Movements were always carried out by participants using their dominant hand. The direction of movement was always indicated by a signal (a change in colour of the target from white to purple) or chosen by the participant.

3.2.5 Data Evaluation

3.2.5.1 Heat Pain Threshold and Tolerance

For HPT and HTOL a mean value of three measures was taken. For HPT the data evaluation process discussed in Chapter 2, section 2A.2.4 was followed to create a *Z*-score value. This was to ensure we could compare to published norms to ensure that the sample had typical heat pain processing. For HTOL mean values were compared across groups to ensure no significant differences were present.

3.2.5.2 Task

The mean NRS rating was calculated for the ratings from multiple blocks for each condition for pain intensity, unpleasantness, and endurance. Outlier trials for the latencies were determined as those <250 and >3,000ms (Claes et al., 2014a) and were eliminated prior to mean calculations. Mean latencies for each CS movement (CS+ and CS-) per condition (reward and no-reward) were calculated for each participant by averaging the movements for each condition. For each condition, the total number of times the CS+ was chosen (i.e., during the choice trials) as an index of decision-making behaviour was calculated (range = 0-

4). This would be the total number of times CS+ was chosen during the choice trials in each block.

Two (Group [ASD/Controls]) *2 (Condition [reward/no-reward]) *2 (CS type [CS+/CS-]) mixed ANOVAs were run to determine group differences in the effects of reward-US on latencies, pain-related fear, and pain-expectancy. Separate 2 (Group [ASD/Controls]) *2 (Condition [reward/no-reward]) ANOVAs were conducted to determine the effects of reward-US on decision making behaviour, pain intensity, unpleasantness, and endurance. Correlations were used to determine if there was any relationship between the painful yet rewarding stimulus, pain avoidance, goal attainment, pain-related fear and pain expectancy.

3.3 Results

T-rests revealed that the ASD group experienced significantly greater restrictive repetitive behaviour patterns $t(11) = 3.218$, $p = .008$ (RBS-R, Lam & Aman, 2007) that were rated as having a greater impact on daily functioning $t(11) = 6.856$, $p = .000$, as well as greater levels of alexithymia $t(11) = 3.520$, $p = .005$ (TAS-20) compared to controls (see table 10).

Table 11:

Descriptive statistics for Questionnaire results for both ASD and Control group

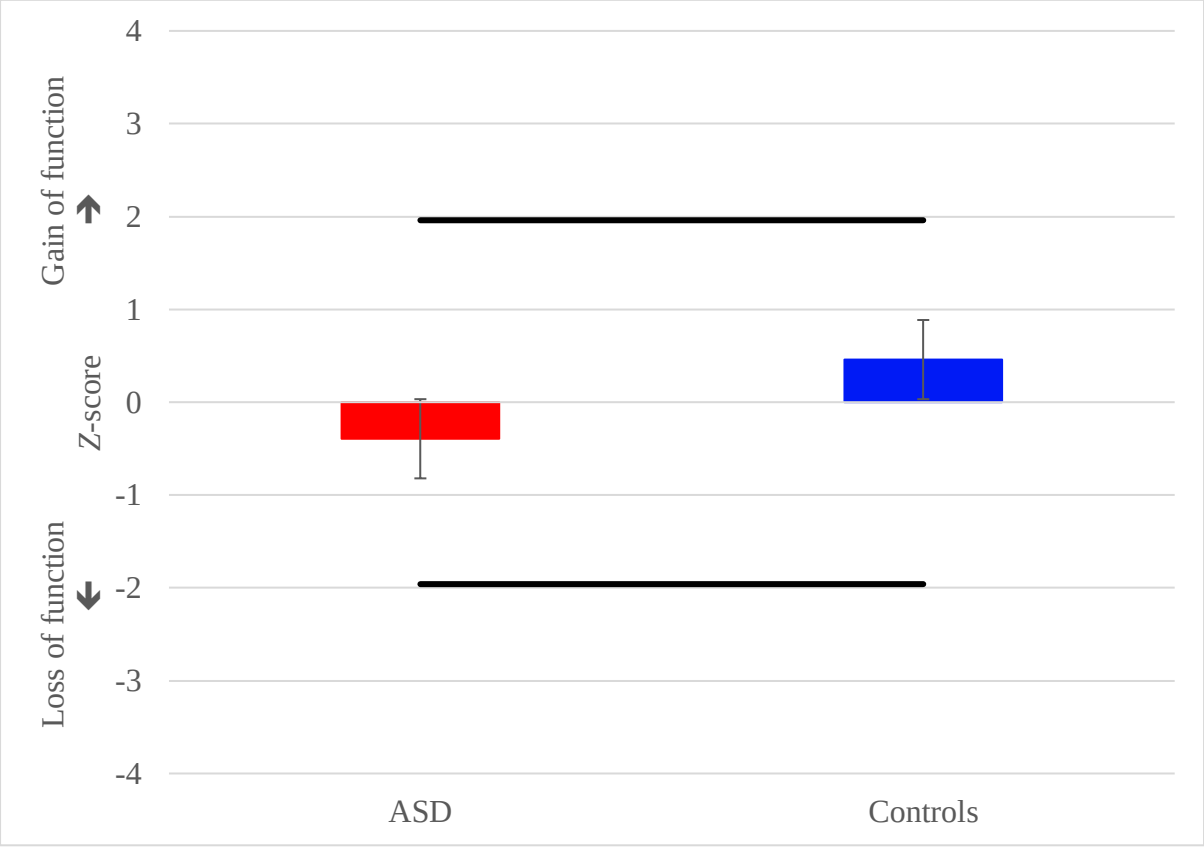
Characteristic	ASD	Controls	Total
No. of participants	8	8	16
Pain Catastrophizing Scale (PCS)	20.50 (5.75)	12.50 (3.35)	16.50 (13.52)
Fear of Pain Questionnaire (FP)	85.50 (9.15)	76.73 (9.73)	81.06 (26.56)
Restrictive Repetitive Behaviour Scale (RRBS)*	41.38 (6.66)	8.13 (3.35)	24.75 (22.41)
RRBS Global Rating*	53.63 (5.05)	13.40 (2.99)	38.15 (23.42)
Toronto Alexithymia Scale (TAS-20)*	61.88 (3.00)	43.75 (2.48)	52.81 (12.01)
The Tampa Scale for Kinesiophobia (TSK)	36.75 (2.72)	32.88 (2.98)	34.81 (8.05)

Note: All values are given as mean (SD). *p<.05. ASD (Autism Spectrum Disorders).

3.3.1 Heat Pain Threshold and Tolerance

Figure 10.

Adjusted Z-scored Heat Pain Thresholds for the ASD and Control group



Note. Adjusted Z-score data for ASD vs. control group for HPT including standard error bars. Any column that extends outside the 95% confidence interval of the normal distribution of healthy subjects (=area between the black lines) signifies sensory changes.

T-test revealed that there were no significant group differences in heat pain threshold (see figure 10) or heat pain tolerance levels (see table 11), showing typical psychophysical response of temperature $t(14) = -1.216$, $p = .244$, $\delta = 0.56$ and $t(14) = -1.310$, $p = .211$, $\delta = 0.65$, respectively. These findings support those of earlier studies, therefore any cognitive effects in this experiment are unlikely a result of altered sensory processing.

Table 12:

Untransformed data values of QST Heat Pain Threshold parameter and Heat Pain Tolerance for ASD and Control group

	ASD	Controls	*p value*	*Effect size (δ)*
Heat Pain Threshold (HPT; ˚C)	43.76 (4.92)	45.98 (3.28)	.244	0.56
Heat Pain Tolerance (HTOL; ˚C)	48.38 (2.72)	49.91 (1.91)	.211	0.65

Note. Group raw data values for each QST parameter and additional sensory tests given as mean ± *SD* to aid understanding in terms of their actual unit of measurement i.e., temperature in Celsius.
All p values and effect sizes given for HPT are for the inferential statistics conducted on transformed data as discussed in Chapter 2 methods section.

3.3.2 Task Self-report measures

A series of 2 (Group [ASD/Controls]) *2 (Condition [reward/no-reward]) *2 (CS type [CS+/CS-]) mixed ANOVAs were run to determine group differences in the effects of reward-US on pain-related fear and pain-expectancy. Separate 2 (Group [ASD/Controls]) *2 (Condition [reward/no-reward]) ANOVAs were conducted to determine the effects of reward-US on pain intensity, unpleasantness, and endurance (see table 12).

Table 13:

Ratings for self-report measures for ASD and Control group, across conditions (No-Reward and Reward) and movement type (CS+/CS-)

		No-reward condition		Reward condition	
	CS type	**ASD**	**Controls**	**ASD**	**Controls**
Pain Expectancy	CS+	5.25 (3.01)	3.88 (1.92)	5.72 (2.47)	4.13 (1.79)
	CS-	2.69 (2.00)	2.50 (2.53)	4.75 (3.05)	1.41 (1.42)
Pain Related Fear	CS+	3.78 (3.43)	2.41 (2.24)	2.81 (3.22)	1.97 (1.85)
	CS-	1.97 (2.13)	1.59 (2.15)	2.75 (2.70)	1.16 (1.46)
Pain Intensity		4.25 (2.34)	2.56 (2.38)	3.41 (2.20)	2.25 (1.83)
Pain Unpleasantness		3.78 (2.47)	2.41 (2.20)	3.19 (2.45)	2.70 (2.15)
Pain Endurance		2.22 (2.33)	1.63 (1.72)	2.09 (2.68)	1.34 (2.18)

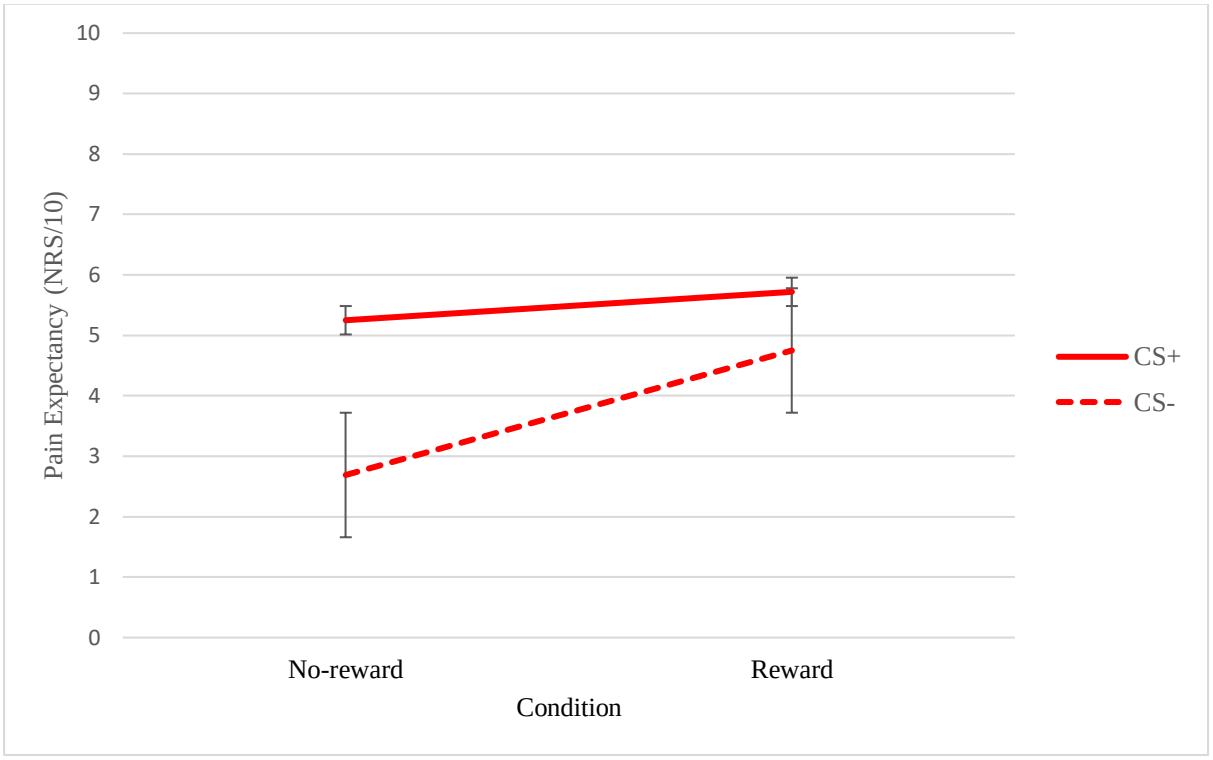
Note. Values are given as mean (*M*) and standard deviation (*SD*) as n/10. ASD (Autism Spectrum Disorder). CS+ indicates movements that are followed by either both the pain-US and the reward-US (Reward condition) or by the pain-US (No-reward condition) in 50% of the trials. CS- indicates a safety movement: that is one that is never followed by a US.

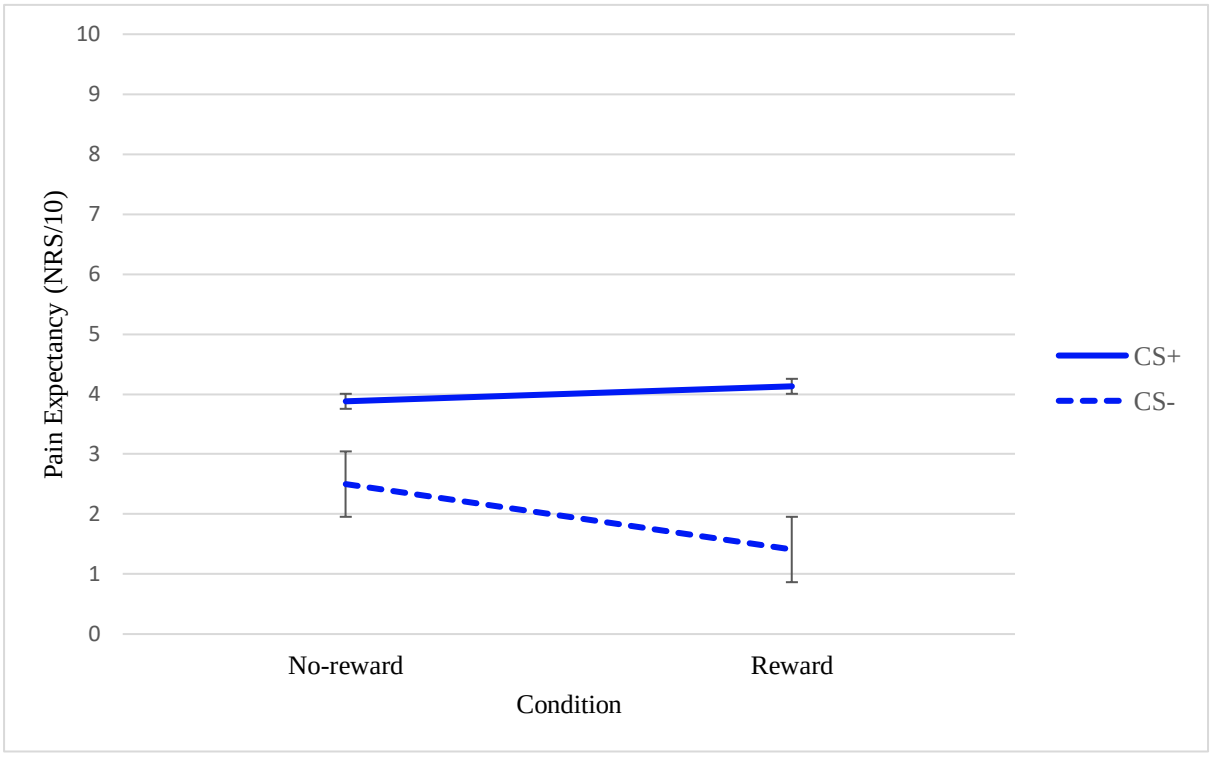
3.3.2.1 Pain Expectancy

There was a significant effect of group revealing that the ASD group had higher pain expectancy ratings than the control group $F(1,14) = 6.547$, $p = .023$, $\eta_p^2 = .319$. There was a significant main effect of CS type $F(1,14) = 8.106$, $p = .013$, $\eta_p^2 = .367$, therefore participants learned that the CS+ movement was associated with the pain-US, and consequently they expected significantly more pain during a CS+ than a CS- movement (see table 13 above for mean values). There was no main effect of condition ($F(1,14) = .483$, $p = .498$, $\eta_p^2 = .033$), a condition*group interaction ($F(1,14) = 1.933$, $p = .186$, $\eta_p^2 = .121$), a CS type*group interaction, $F(1.14) = .044$, $p = .837$, $\eta_p^2 = .033$ or a condition*movement interaction ($F(1,14) = .026$, $p = .873$, $\eta_p^2 = .002$). There was a trend towards significance for the condition*CS type*group interaction $F(1,14) = 3.647$, $p = .077$, $\eta_p^2 = .207$. This indicates a trend for pain expectancy for CS type differing according to condition, and that these ratings were different in the ASD group compared to controls (see figure 11). This pattern of findings shows that contingency learning occurred due to the pain for controls, as their ratings for pain expectancy were higher for a painful movement than a non-painful movement and occurred due to the presence of the reward for the ASD group, as ratings increased across conditions.

Figure 11.

Mean pain expectancy ratings (NRS/10) for movements (CS+/CS-) in both No-reward and Reward conditions for the ASD group (red line chart) and Control group (blue line chart)





Note. Shows the three-way interaction for condition*movement*group for pain expectancy. Pain expectancy is given as Mean (NRS/10). CS+ indicates movements that are followed by either both the pain-US and the reward-US (Reward condition) or by the pain-US (No-reward condition) in 50% of the trials. CS- indicates a safety movement: that is one that is never followed by a US.

3.3.2.2 Pain-Related Fear

There was no significant effect of group ($F(1) = 1.097$, $p = .313$, $\eta_p^2 = .073$), nor any significant main effects of condition $F(1,14) = .579$, $p = .459$, $\eta_p^2 = .040$, or CS type $F(1,14) = 2.424$, $p = .630$, $\eta_p^2 = .148$, for pain-related fear indicating that fear was not influenced by either reward-US or pain-US. Non-significant interactions were found for condition*group ($F(1,14) = .243$, $p = .630$, $\eta_p^2 = .017$), CS type*group ($F(1,14) = .012$, $p = .913$, $\eta_p^2 = .001$), condition*CS type ($F(1,14) = 1.927$, $p = .187$, $\eta_p^2 = .121$) and condition*CS type*group ($F(1,14) = 1.927$, $p = .187$, $\eta_p^2 = .121$), indicating that for pain-related fear, not only was this not influenced by the reward-US or the pain-US, but that groups did not differ.

3.3.2.3 Pain Intensity and Unpleasantness

For pain intensity there was a trend towards a significant main effect for conditions, ($F(1,14) = 3.897$, $p = .068$, $\eta_p^2 = .218$), indicating that there was a trend for the reward-US to attenuate pain intensity, as ratings reduced from no-reward condition to reward condition (see table 3). There was a non-significant interaction for condition*group ($F(1,14) = .823$, $p = .380$, $\eta_p^2 = .056$), indicating that there was no group differences in pain intensity across conditions.

There was no main effect of condition for unpleasantness ($F(1,14) = 1.734$, $p = .209$, $\eta_p^2 = .110$) or endurance ($F(1,14) = 2.429$, $p = .141$, $\eta_p^2 = .148$), nor were there significant interactions for condition*group for either unpleasantness ($F(1,14) = .469$, $p = .505$, $\eta_p^2 = .032$) or endurance ($F(1,14) = .359$, $p = .558$, $\eta_p^2 = .025$), indicating reward-US did not attenuate these.

3.3.3 Task Behavioural Responses

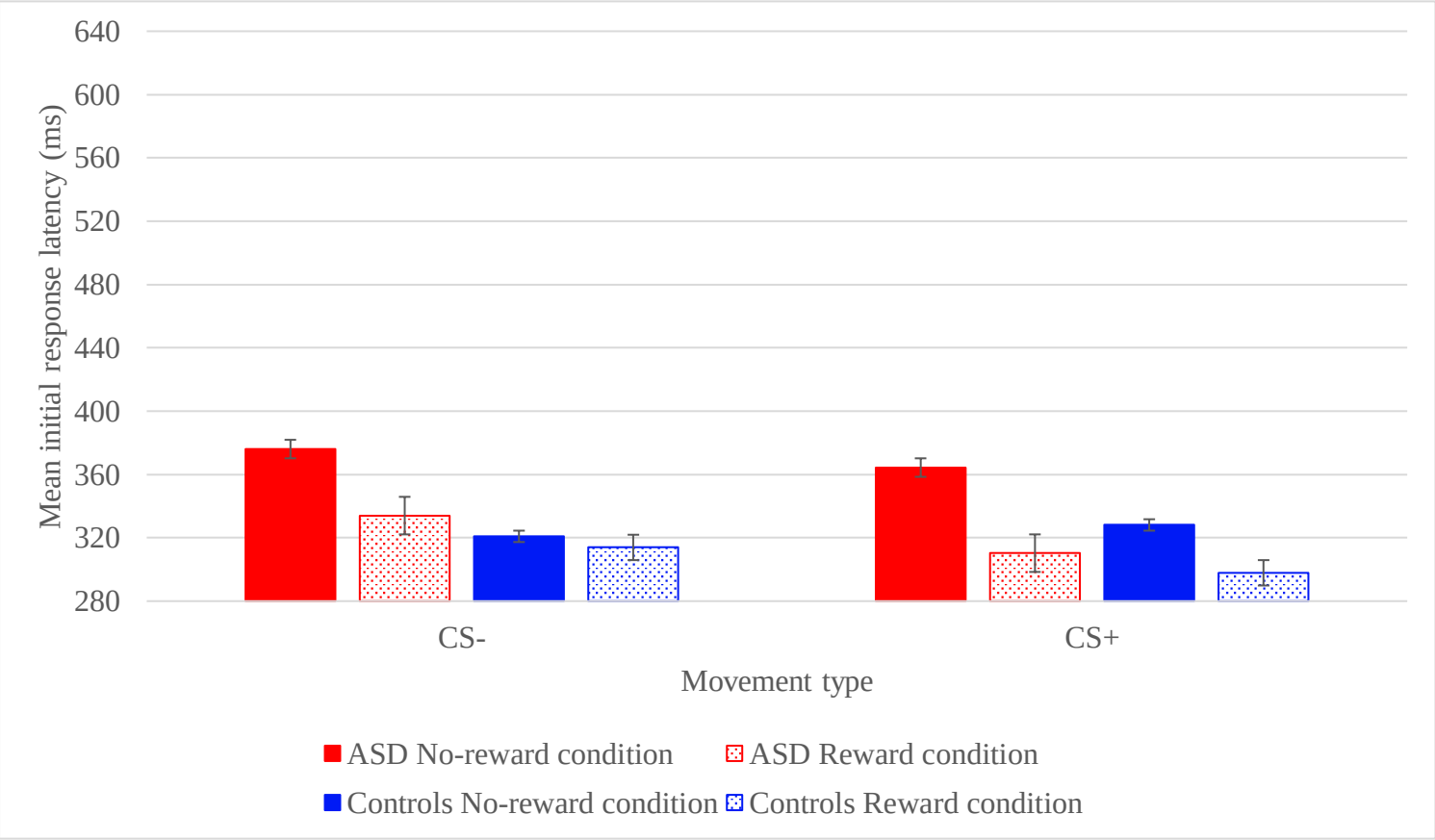
Several 2 (Group [ASD/Controls]) *2 (Condition [reward/no-reward]) *2 (CS type [CS+/CS-]) mixed ANOVAs were run to determine group differences in the effects of reward-US on latencies: initial response latency, response latency and response time.

3.3.3.1 Initial Response Latency

There was no significant effect of group $F(1,14) = .149$, $p = .705$, $\eta_p^2 = .011$. There was no significant main effect of condition ($F(1,14) = 2.646$, $p = .126$, $\eta_p^2 = .159$) or CS type ($F(1,14) = .591$, $p = .455$, $\eta_p^2 = .404$). Neither were interactions significant; condition* group ($F(1,14) = .516$, $p = .484$, $\eta_p^2 = .036$), CS type* group ($F(1,14) = .213$, $p = .652$, $\eta_p^2 = .015$), condition*CS type ($F(1,14) = .458$, $p = .509$, $\eta_p^2 = .032$) and condition*CS type*group ($F(1,14) = .046$, $p = .833$, $\eta_p^2 = .003$). Indicating that within the defined area being measured, neither the reward-US nor pain-US impacted the reflex movement, i.e., initial response latency for groups (see figure 12).

Figure 12.

Mean initial response latencies (given in ms) for No-Reward and Reward conditions and movements (CS+/CS-) for both ASD and Control group



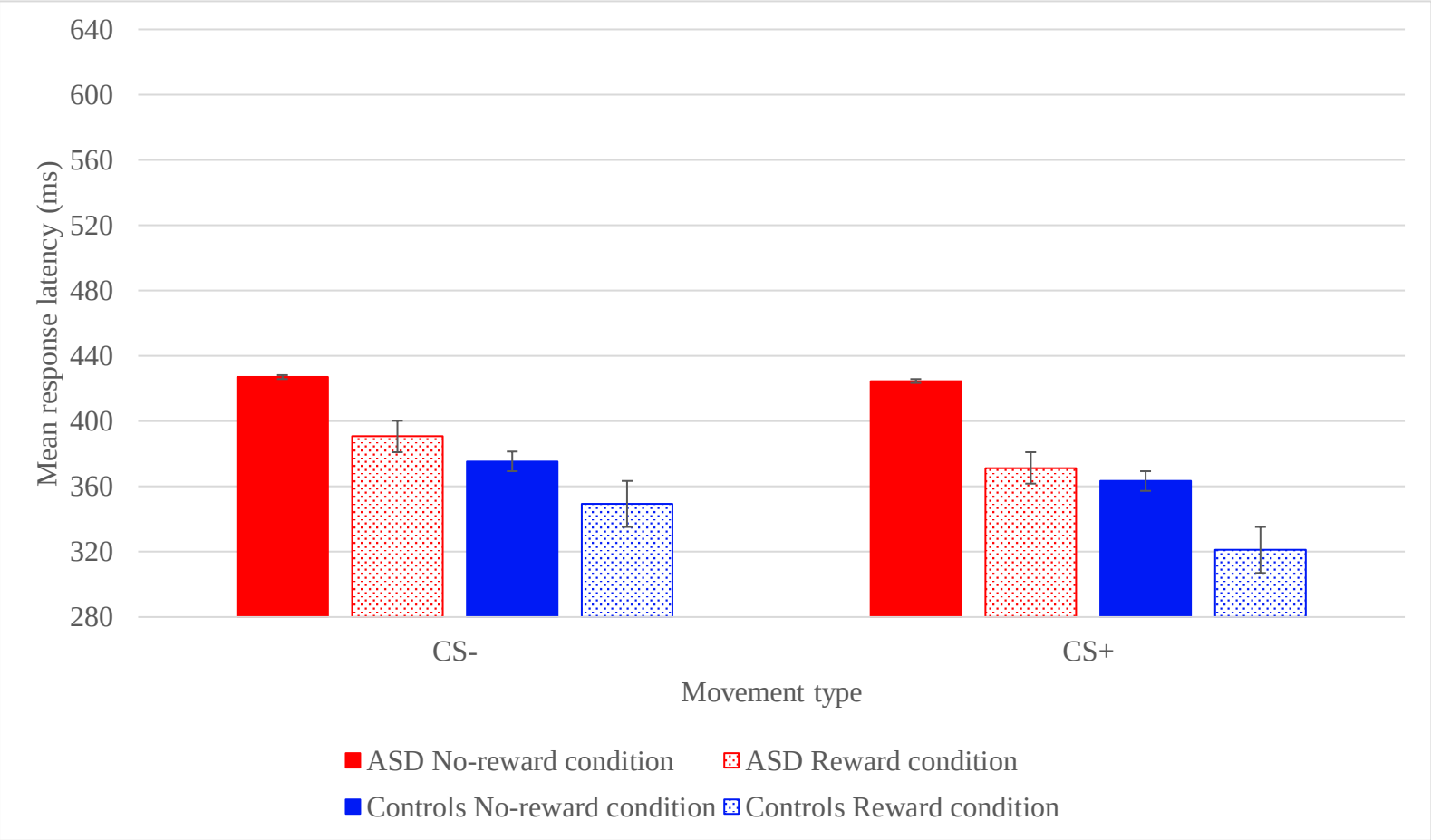
Note. Mean latencies for CS type (CS+/CS-) for both conditions (reward/no-reward) for both groups (ASD/controls). Values given as mean (ms) including standard error bars. CS+ indicates movements that are followed by either both the pain-US and the reward-US (Reward condition) or by the pain-US (No-reward condition) in 50% of the trials. CS- indicates a safety movement: that is one that is never followed by a US.

3.3.3.2 Response Latency

There was no significant effect of group $F(1,14) = .448$, $p = .514$, $\eta_p^2 = .031$. There was no main effect of condition ($F(1,14) = 2.914$, $p = .110$, $\eta_p^2 = .110$) or CS type ($F(1,14) = 1.306$, $p = .272$, $\eta_p^2 = .272$). Neither were interactions significant; condition* group ($F(1,14) = .053$, $p = .821$, $\eta_p^2 = .036$), CS type* group ($F(1,14) = .118$, $p = .737$, $\eta_p^2 = .015$), condition*CS type ($F(1,14) = .543$, $p = .473$, $\eta_p^2 = .032$) and condition*CS type*group ($F(1,14) = .000$, $p = .987$, $\eta_p^2 = .987$). Indicating that within the defined area being measured, neither the reward-US nor pain-US impacted the decision to move i.e., the response latency for groups was similar (see figure 13).

Figure 13.

Mean response latencies (given in ms) for No-Reward and Reward conditions and movements (CS+/CS-) for both ASD and Control group



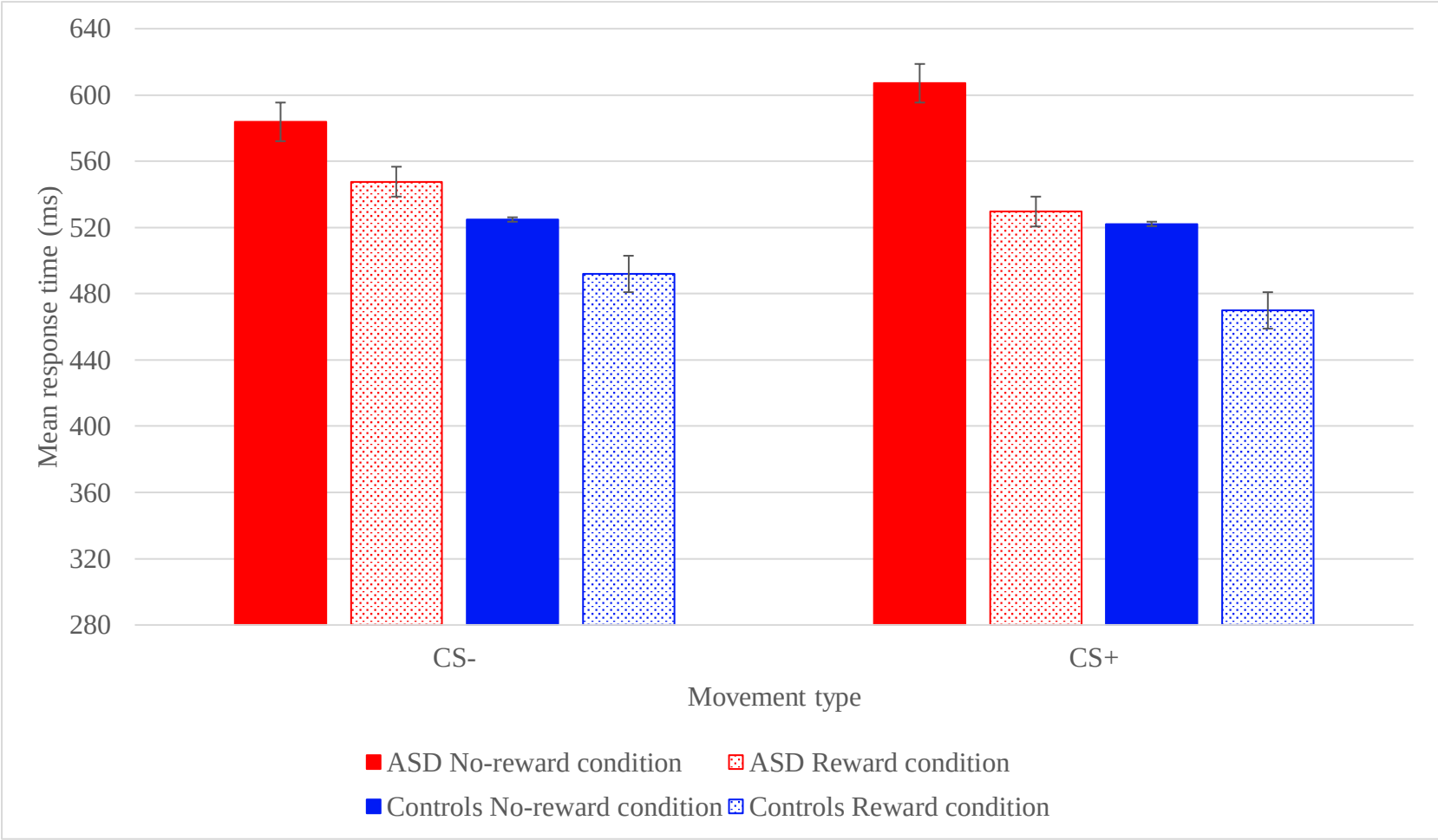
Note. Mean latencies for CS type (CS+/CS-) for both conditions (reward/no-reward) for both groups (ASD/controls). Values given as mean (ms) including standard error bars. CS+ indicates movements that are followed by either both the pain-US and the reward-US (Reward condition) or by the pain-US (No-reward condition) in 50% of the trials. CS- indicates a safety movement: that is one that is never followed by a US.

3.3.3.3 Response Time

For the response time, i.e. the time it takes to reach the target and complete a signalled movement, there was no effect of group $F(1,14) = .533$, $p = .478$, $\eta_p^2 = .037$. There was a significant main effect of condition $F(1,14) = 6.279$, $p = .025$, $\eta_p^2 = .310$. Indicating that the reward-US influenced participants to respond faster representing an increase in motivation (see figure 14). Although they were not influenced by the pain-US as a non-significant main effect of CS type was found $F(1,14) = .182$, $p = .676$, $\eta_p^2 = .013$. There were no significant interactions for condition*group ($F(1,14) = .129$, $p = .725$, $\eta_p^2 = .009$), CS type*group ($F(1,14) = .432$, $p = .522$, $\eta_p^2 = .030$), condition*CS type ($F(1,14) = 1.921$, $p = .187$, $\eta_p^2 = .121$) and condition*CS type*group ($F(1,14) = .252$, $p = .623$, $\eta_p^2 = .018$).

Figure 14.

Mean response time (given in ms) for No-Reward and Reward conditions and movements (CS+/CS-) for both ASD and Control group



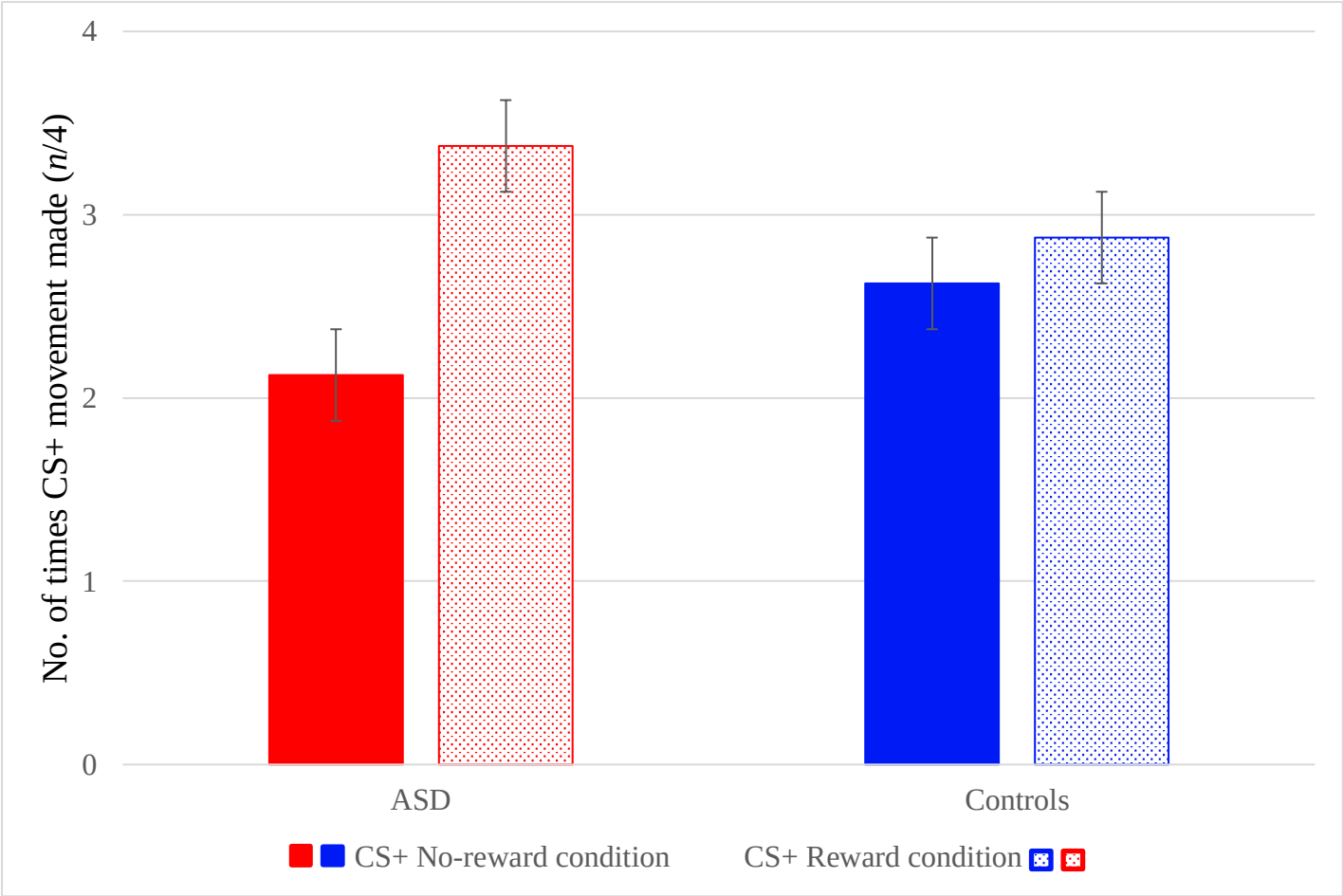
Note. Mean latencies for CS type (CS+/CS-) for both conditions (reward/no-reward) for both groups (ASD/controls). Values given as mean (ms) including standard error bars. CS+ indicates movements that are followed by either both the pain-US and the reward-US (Reward condition) or by the pain-US (No-reward condition) in 50% of the trials. CS- indicates a safety movement: that is one that is never followed by a US.

3.3.4 Decision Making Behaviour

A 2 (Group [ASD/Controls]) 2 (Condition [reward/no-reward]) mixed ANOVA was run on the number of CS+ (painful paired with reward-US) movements participants performed during choice trials in both conditions. There was a trend towards significance for condition $F(1,14) = 4.065$, $p = .063$, $\eta_p^2 = .225$ and a no significant interaction for condition*****group $F(1,14) = 1.806$, $p = .200$, $\eta_p^2 = .114$ (see figure 15). More specifically, 90% of the sample chose to make more than one painful yet rewarding movement during the reward condition, with 50% of the sample choosing to make all four painful yet rewarding movements. Indicating that there was a trend for all participants choosing to make a painful movement more often when there was a concurrent reward (reward condition, see figure 15).

Figure 15.

Mean number of movements (n/4) chosen in the No-Reward and Reward condition for ASD and Control group



Note. Given as *n* (number of /4) CS+ movements made during choice trials for both groups (ASD/Controls) across conditions (reward/no-reward). CS+ indicates movements that are followed by either both the pain-US and the reward-US (Reward condition) or by the pain-US (No-reward condition) in 50% of the trials. CS- indicates a safety movement: that is one that is never followed by a US.

3.3.5 Additional Analysis

Correlations were used to determine if there were any relationship between the painful yet rewarding stimulus (CS+), and the predictors; self-reported pain avoidance, self-reported goal attainment and pain-related fear. There were no significant correlations for the entire sample for the number of times a CS+ movement was made during choice trials and avoidance, goal attainment, pain-related fear, or pain expectancy (see table 13).

Table 14:

Descriptives and correlations for the no of CS+ choice movements made during the Reward condition and self-report measures for the entire sample

Variable no. and descriptor	*M (SD)*	2	3	4	5
1. No. of CS+ movements performed in the reward condition	3.125 (1.204)	.326	.100	.010	.016
2. Avoidance	1.750 (2.295)	1.00	.010	.571*	.330
3. Goal attainment	6.310 (3.535)		1.00	.402	.107
4. Pain-related fear of CS+	2.390 (2.574)			1.00	.456
5. Pain expectancy of CS+	4.922 (2.257)				1.00

Note. Values given as mean (*M*) and standard deviation (*SD*). *$p<.05$. ASD (Autism Spectrum Disorder). CS+ indicates movements that are followed by either both the pain-US and the reward-US (Reward condition) or by the pain-US (No-reward condition) in 50% of the trials. CS- indicates a safety movement: that is one that is never followed by a US.

There was a significant positive moderate correlation between avoidance and pain related fear ($r = .571$, $p = .021$), indicating that as desire to avoid the pain-US increased so did the fear related to said pain-US. Further individual group analysis correlations indicated that this significant correlation is driven by the ASD group, indicating a stronger relationship between fear and desire to avoid the stimulus ($r = .706$, $p = .05$) than healthy controls, which yielded a non-significant correlation ($r = -.038$, $p = .928$; see table 5). For the control group, there was a significant strong positive correlation for goal attainment and pain expectancy, indicating that as the desire to achieve the goal (earn the reward-US) increased so did the

expectancy of pain (r = .788, p = .020), therefore the contingencies were learned much more strongly within the control group (see table 14).

Table 15:

Descriptives and correlations for the number of CS+ choice movements made during the reward condition and self-report measures for ASD and Control group

Variable no. and descriptor		*M* (*SD*)	2	3	4	5
1. No. of CS+ movements performed in the reward condition	ASD	3.375 (.744)	.329	.547	.421	-.051
	Controls	2.875 (1.553)	.426	-.061	-.411	-.096
2. Avoidance	ASD	3.000 (2.673)	1.00	.086	.706*	.325
	Controls	.500 (.756)	1.00	-.229	-.038	-.581
3. Goal attainment	ASD	6.380 (3.114)		1.00	.322	-.538
	Controls	6.250 (4.132)		1.00	.593	.788*
4. Pain-related fear of CS+	ASD	2.813 (3.218)			1.00	.510
	Controls	1.969 (1.854)			1.00	.244
5. Pain expectancy of CS+	ASD	5.179 (2.466)				1.00
	Controls	4.125 (1.788)				1.00

Note. Values given as mean (*M*) and standard deviation (*SD*). *p<.05. ASD (Autism Spectrum Disorder). CS+ indicates movements that are followed by either both the pain-US and the reward-US (Reward condition) or by the pain-US (No-reward condition) in 50% of the trials. CS- indicates a safety movement: that is one that is never followed by a US.

3.3.6 Habituation Observation Check

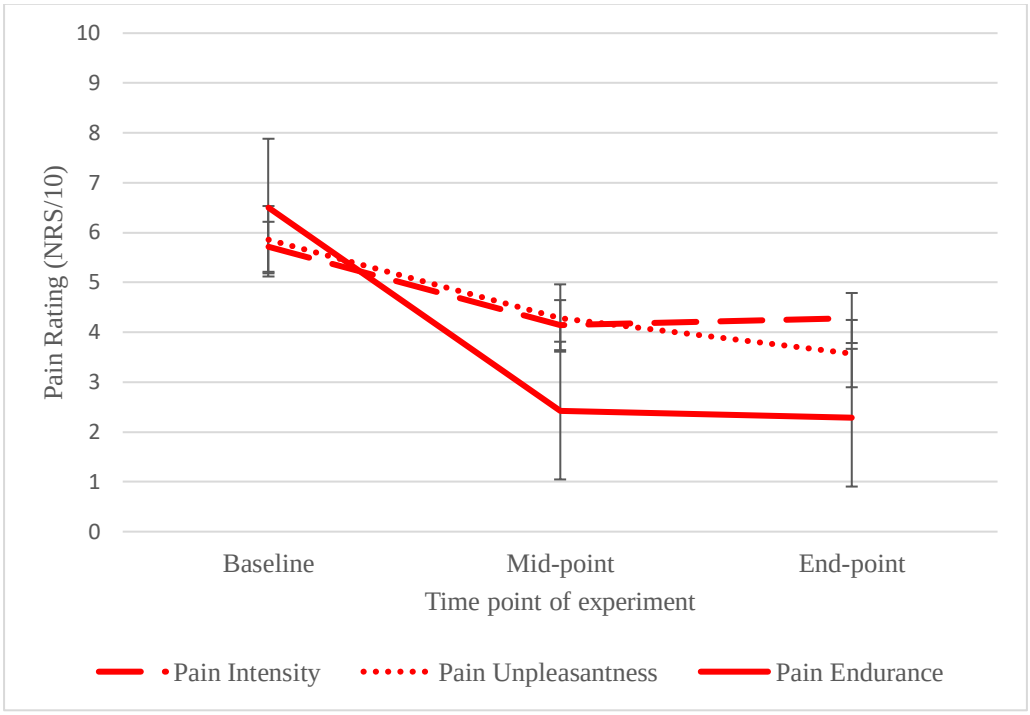
A 2* (Group [ASD/Controls]) *3 (Pain rating [intensity/unpleasantness/endurance]) *3 (time [baseline/mid-point/endpoint]) mixed ANOVA was run to determine whether habituation to the stimuli and to determine if there were group differences in terms of this habituation and to confirm statistically an observation made during the experiment.

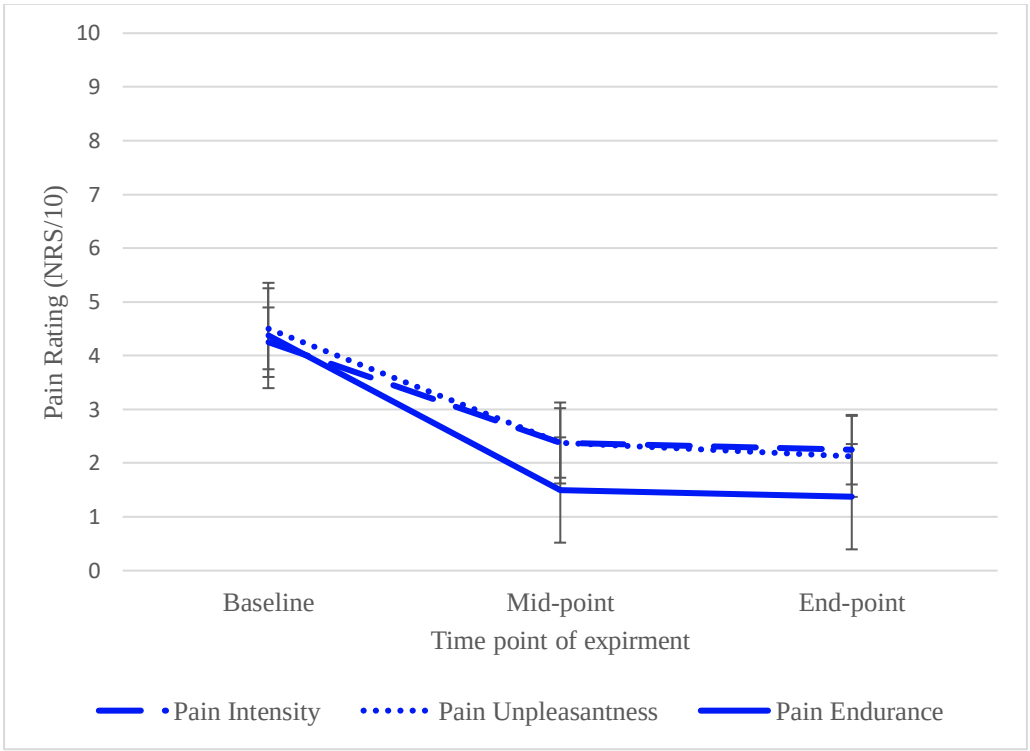
There was no significant effect of group $F(1,13) = 2.926$, $p = .111$ $\eta_p^2 = .184$, indicating that pain ratings at each time point of the experiment were similar across both

groups. There was a significant main effect of pain rating type ($F(2,52) = 8.363$, $p = .002$, $\eta_p^2 = .391$) and time ($F(2,52) = 17.763$, $p = .000$, $\eta_p^2 = .577$). Contrasts revealed that there was a significant difference in ratings for intensity ($F(2,52) = 15.227$, $p = .002$, $\eta_p^2 = .539$) and unpleasantness ($F(2,52) = 10.562$, $p = .006$, $\eta_p^2 = .448$) verses tolerance, and a difference in ratings between baseline and the end point of the experiment ($F(2,52) = 20.044$, $p = .001$, $\eta_p^2 = .607$). There was a significant pain*time interaction ($F(2,52) = 5.213$, $p = .001$, $\eta_p^2 = .286$), indicating that the types of pain ratings at the three time points during the experiment differed. Contrasts were performed comparing each time point to the last category or "end point" across each type of pain rating compared to the category of endurance. The first contrast revealed a significant interaction when comparing pain intensity to pain endurance at baseline to "end-point" ($F(1,13) = 11.607$, $p = .005$, $\eta_p^2 = .472$). Contrasts comparing pain intensity to pain endurance at "mid-point" to "end point" were non-significant ($F(1,13) = .730$, $p = .408$, $\eta_p^2 = .053$). As were the contrasts comparing unpleasantness to tolerance at both baseline to "end point" ($F(1,13) = 3.194$, $p = .097$, $\eta_p^2 = .197$) and "mid-point" to "end point" ($F(1,13) = 1.042$, $p = .326$, $\eta_p^2 = .074$). These findings show that both groups habituated to the pain and did so quickly, and they are more able to endure the pain after experiencing it at baseline, despite the intensity and unpleasantness of the stimuli remaining consistent throughout the experiment (see figure 16).

Figure 16.

Mean pain intensity, unpleasantness, and endurance ratings (NRS/10) at baseline, midpoint, and endpoint of the experiment for ASD (red line chart) and control groups (blue line chart)





Note. Mean pain intensity, unpleasantness (given as NRS/10) at the baseline, mid-point, and endpoint of the experiment for both groups (ASD/controls). Values given as mean (NRS) including standard error bars. CS+ indicates movements that are followed by either both the pain-US and the reward-US (Reward condition) or by the pain-US (No-reward condition) in 50% of the trials. CS- indicates a safety movement: that is one that is never followed by a US.

3.4 Discussion

The current experiment investigated whether autistic individuals had a greater attenuation of pain avoidance behaviours, using the volitional joystick task (VJT) paradigm (Claes et al., 2014). In the reward condition, a reward accompanied a painful movement, thus installing a competing goal. On some trials participants were instructed to choose whether to perform either the painful yet rewarding movement or the no pain safety movement. Therefore, avoidance tendencies; the avoidance of pain and the approaching a reward or negating the pain to collect the reward, could be measured. This experiment is the first of its kind to investigate pain processing in ASD from a motivational perspective, in terms of competing goals and avoidance behaviours. The entire sample were no quicker at completing a no-pain movement than a painful or painful yet rewarding movement (dependent on condition), therefore not replicating the findings of Claes et al., (2014). Given this, but more specifically that our control group did not show pain motivation, interpretability and generalizability of findings is limited, particularly when determining if autistic individuals differ or not from controls. It does, however, highlight important considerations - for failure to replicate basic paradigms points to a range of potential confounding variables, that should be reflected upon and considered.

One potential explanation for these findings, is in relation to the stimuli used. This experiment utilised a CHEPS thermal pain stimulus in order to activate both Aδ and C-fibres (Granovsky et al., 2005) rather than the electrical stimulus utilised in the Claes et al., (2014). The choice to use this was derived from contradictory findings that there are potential peripheral changes specific to electrocutaneous pain in ASD (see Chapter 2A.3.2 Bird et al., (2010); Fan et al., (2014)), from contradictory methodologies, rendering electrocutaneous stimuli unreliable in this population. The evidence for heat pain perception was more

consistent and reliable, and as the CHEPS stimulation could activate similar pathways it was deemed a more reliable method for the ASD population. Further analysis was conducted on inspection of the main findings and showed that from baseline to end of experiment a significant decrease in endurance levels were reported, therefore both groups were better able to endure the thermal stimulus. This may be the result of thermal pain habituation, whereby nociceptors habituate to the stimulus over time (Bauch et al., 2017). Furthermore, although the intensity and unpleasantness of the stimulus was higher than endurance, all three self-report ratings dropped over the duration of the experiment, supporting this notion of habituation. Although initially thermal pain was suspected to be more reliable specifically for the ASD group, electrical pain may be more suitable to this type of task to maintain stimulus effect and therefore influence motivation during a cognitively challenging task because of its high degree of temporal and intensity acuity (Ng et al., 2020). Electrocutaneous stimulation affects the membrane potential of all cells leading to the activation of all receptors, resulting in a complex sensation (Lee et al., 2000). This complex sensation and ability for the stimuli to maintain the selected intensity from onset to offset may be more relevant to accessing pain motivation over a period of time and during a task that is cognitively demanding. It may, therefore, be prudent for future studies to revert to using this stimulation and utilising the methodology employed here of checking for changes in pain perception prior to the VJT paradigm is implemented. Although there are currently no published normative values to ensure that levels are within a clinically relevant normal range, comparing across groups to ensure there are no differences will still provide relative confidence in findings from the VJT paradigm.

Despite replication failure for response times (all three measures), similarly, to Claes et al., (2014) and Meulders et al., (2011) it was found that both groups show less avoidant decision-making behaviour when there is a competing goal present. Although, this was only

trend level data in this instance, it is a possibility that this indicates that the ASD group's fear avoidance, and pain motivation processing is intact or at the very least comparative to the control group (Claes et al., 2014, 2016; Crombez et al., 2012; Meulders et al., 2011; Vlaeyen et al., 2009). In this circumstance adding a monetary reward has the potential to attenuate avoidance behaviours in ASD. Previous research has shown that using valuable incentives increase pain tolerance and have the ability to increase motivation towards a reward (Cabanac, 1986; Gandhi et al., 2013), however, these studies have not focussed on the ASD population. Monetary rewards in ASD have shown both typical processing (Delmonte et al., 2012; McPartland et al., 2012) and a diminished response in reward neural circuitry (Scott-Van Zeeland et al., 2010). These studies focus on reward circuitry rather than the reward in the context of pain, and as such our results appear to support the notion that monetary rewards are ecologically valid for this population and act as a competing goal in attenuating pain. Avoidance behaviour in ASD is therefore likely to be influenced by this competing goal even without changing the pain-related fear, which is considered to be the aspect that typically drives the pain motivation (Crombez et al., 2012; Hasenbring & Verbunt, 2010; Vlaeyen & Linton, 2012); and is similar to the response found in neurotypicals (Claes et al., 2014a).

Pain expectancy for the ASD group was increased during the reward condition where the monetary reward was introduced, regardless of whether it was a movement associated with pain or a non-pain movement. Meaning the ASD group showed contingency learning of a lesser degree than the control group. They showed an increase in ratings from the no-reward condition to the reward condition for both movements, indicating that the reward influenced pain expectancy. Further investigation is required to understand why a reward may have such an effect within an autism population. This is especially important considering the control group, had similar pain expectancies across the conditions for a

movement that was paired with pain than a no-pain movement, which is a typical response for this methodological paradigm (Claes et al., 2014, 2016; Vlaeyen & Linton, 2012).

Results also indicated that the ASD group had an overall greater fear and greater desire to avoid the stimulus. Such findings may be attributed to levels of anxiety found in ASD (see van Steensel & Heeman, (2017) for review; South & Rodgers, (2017)), which is shown to influence pain perception (Ocañez et al., 2010; Quartana et al., 2009; Thompson et al., 2016). Additionally, affective states in ASD can predict pain behaviours (Failla et al., 2020; Garcia-Villamisar et al., 2019), in particular, pain anxiety was associated with increased pain ratings (Failla et al., 2020) and general anxiety symptomology found to mediate the relationship between autism traits and pain behaviours, as defined by the non-Communicating Adults Pain Checklist (Garcia-Villamisar et al., 2019).

Accurate assessment of anxiety in ASD is challenging because of symptom overlap with other psychiatric disorders (Vasa & Mazurek, 2015), therefore, despite our sample not having a formal anxiety diagnosis, undiagnosed anxiety may have resulted in the larger variance observed. Such variability could preclude group and main effect differences, as reported. Since the paradigm itself relied on fear and the desire to avoid the painful stimulus, undiagnosed anxiety is likely to impact on results, increasing pain sensitivity (Garcia-Villamisar et al., 2019) or an inability to inhibit the fear response (Norrholm & Jovanovic, 2018). For example, in its extreme form, generalization (the phenomena whereby non-reinforced stimuli elicit fear responses when they resemble the CS+; conditioned stimulus), can lead to poorer discrimination abilities so that aversive and safety signals are not processed appropriately (Dunsmoor & Paz, 2015). Individuals are therefore, unable to supress or inhibit the fear response even under safe conditions, such as the safety movement in this study (CS-), as has been reported in PTSD samples (Milad et al., 2009; Morey et al.,

2015). Similar to the findings from this thesis, Jovanovic et al., (2009), reported that those with PTSD compared to traumatised controls had impaired fear inhibition despite all participants, regardless of diagnosis, reporting contingency learning. Demonstrating that the PTSD participants were aware of the safety movement but were unable to supress their fear at a physiological level (as measured by their startle response). It is possible, that much like this PTSD sample, our ASD group were aware that a movement in the opposite direction to a conditioned stimulus movement was safe, but were unable to supress their fear, as represented by the non-significant main effects of movement type and condition despite expecting pain for the appropriate movement. Although fear conditioning is generally an adaptive form of learning, it can become a source of pathology when anxious reactivity to a conditioned stimulus persists in the absences of a conditioned/unconditioned stimulus contingency (Lissek et al., 2005). It is possible that maladaptive fear or pathological anxiety may serve as a common feature of fear-related psychopathology (Jovanovic et al., 2012) and could additionally indicate an anxiety phenotype in ASD related to pain responses.

However, for the entire sample, pain expectancy was higher for painful movements than for no-pain movements, indicating contingency learning for the entire sample. The reward attenuated pain and did not influence fear of pain, since both groups were quicker to complete a movement in the reward condition compared to the no-reward condition, and there was no change in pain-related fear scores regardless of the presence of the reward. Differences in findings may be attributed to differences in methodologies or contextual factors. For example, Failla et al., (2020) used a pain rating curve in which 7 different heat stimuli, all above 40◦C, were applied for five seconds each in a pseudo random order in a laboratory. As well as a sustained heat pain task, were alternating heat temperatures (42◦C and 46◦C) were presented at the same site for 21 seconds each. Garcia-Villamisar et al., (2019) observed a painful dental procedure and vaccination. Where both environments were

specifically focussed on either the painful stimuli or the dental procedure itself. Therefore, the number of demands or goals that could occur simultaneously were not as evident as in this paradigm, where a reward acted as a competing goal. Suggesting that the impact of anxiety of pain could be contextual and that this impact could be reduced by other contextual factors, namely a rewarding goal. Measures of anxiety also differed, and so further investigation is required to delineate this complex relationship between fear, anxiety, and pain response in ASD. Participants also on average also chose to negate the pain in order to receive the reward nearly 3 out of the 4 times the choice was offered, and there was a trend towards this being greater in the ASD group than in controls. Additionally, in such paradigms, controls should be able to supress the fear response during CS- presentations, the lack of group differences could suggest that our controls also shared a similar over generalization to stimuli. However, since there were no group differences reported and mean values followed the same patterns of response, across groups and in line with the pattern of response reported by Claes et al., (2014), it is likely that findings are weakened by sample size and power issues.

The sample size was small resulting in the risk of type II errors and therefore a limitation to this experiment, although power analysis indicated that this sample size was sufficient to yield 60% power. As this is also paired with weak effect sizes for findings such a response times, which determine whether the experimental paradigm measures what it proposed to, it is difficult to determine if the outcomes are true findings. In this instance, it is difficult to determine whether pain motivation is intact, or whether it differs in autistic individuals. ASD research is fraught with small sample sizes (Cascio et al., 2008; Fründt et al., 2017). It therefore is an ongoing issue within the field of ASD research, and this experiment appears to be of no exception. Recruitment of this population has several issues. In particular, the rapport required to engage participants takes longer and more time needs to

be spent in terms of managing nervousness and anxiety, especially when the experiment requires coming to a strange environment where large machinery may also impact on state anxiety. Additionally, the type and duration of such an experiment means that frequently those recruited need to be at the functioning end of the spectrum and therefore reduces the number of those able to recruit. This has been discussed in the previous Chapter 2 and has similar implications to the previous experiment in terms of generalizability to the wider autism spectrum. These issues alongside the ongoing small sample size in the literature weakens the ability to provide reliable results that can support or refute those currently reported. Working across laboratories using similar methodologies to create robust studies that can either replicate or to create larger sample sizes that are frequently more desired could be a beneficial consideration for future studies (Button et al., 2013; Christley, 2010).

Variability becomes an increasing issue with smaller sample sizes such as this, particularly when paired with larger standard deviations, resulting in a decreasingly representative sample (Goulet & Cousineau, 2019). In this sample, larger standard deviations are reported for the ASD group in the reward condition compared to controls. Although for the non-reward conditions, standard deviations were comparative across groups. This might provide further support of the earlier discussion about the reward acting as a conduit for contingency learning in ASD. Although again this would require further testing and consideration. Despite this, large standard deviations are not uncommon in ASD research, as there is large heterogeneity across the spectrum (Lai et al., 2013). Together, this may preclude differences in pain motivation being detected. These attempts, therefore, should be seen as exploratory, used in the cumulative development of measurement procedures (Irvine, 2021). Producing replications, even those considered as failing to replicate due to different findings, advances theory by confronting existing understanding to develop new understanding, especially when the existing understanding is weak (Nosek & Errington,

2020). A recommendation would be to obtain a measure of general anxiety, potentially rather than a pain specific anxiety measure, or both together. This would control for potential inflation of pain responses due to undiagnosed anxiety, and aid in determining if there is an over generalisation of fear response linked to anxiety in ASD. However, consideration of participants is also paramount, and this choice should be weighed against the duration, since lengthy studies can lead to higher attrition rates, in already limited sampling.

Another related limitation is the inability to examine individual differences within the current paradigm. The importance of individual differences was highlighted in the previous Chapter 2 where results showed greater inter-individual variability within the ASD group. The general heterogeneity and variability within the spectrum of ASD, each with distinct aetiologies, means the typical group analyses may not be advantageous to understanding this spectrum condition (Lai et al., 2013). However, there is little suggestion of research relevant solutions. There appears a need at the clinical level for a more fine-grained taxonomy for autism that may result in clearer research related to such subgroups.

To conclude, this experiment investigated pain in ASD from a new methodological stance, one of a motivational, fear-avoidance and multiple goal context. Findings are tentative and definitive conclusions difficult to draw. However, this does provide a strong methodological contribution to this area of research. This first of its kind this experiment has highlighted some interesting areas to consider for future development. For example, it may be important to consider that pain motivation and avoidance behaviours are indeed functioning typically in this population, and therefore, establishing this through replication and further investigation is an important step in further explaining the observational and anecdotal claims of altered behaviour. Furthermore, individual differences are hard to consider within the current protocol and it may therefore be prudent in light of findings from

our earlier experiment, to develop this further. Additionally, electrocutaneous stimuli may need to be implemented and necessary, in order to maintain the effects of the stimulus throughout the experiment and to avoid habituation. Lastly, research is typically fraught with small sample sizes (Cascio et al., 2008; Duerden et al., 2015; Fründt et al., 2017) and adding fundamental power problems. It may, therefore, be important to work across laboratories, in order to fully investigate experimentally this potential source of explanation of pain in ASD, whereby improving on sample size and providing power.

Chapter 4. Expression of Acute Experimental Pain in Autism Spectrum Disorder

Chapter 4. Introduction

Research has indicated potential individual differences in peripheral processing of nociceptive stimuli in ASD but not global systematic, population level changes in pain perception (see Experiment 1 and 2, Fründt et al., (2017); Vaughan et al., (2019)). Additionally, Experiment 3 in Chapter 3 investigated pain motivation in ASD using a volitional joystick task and results tentatively support the notion that pain motivation and avoidance behaviours appear to function typically in this population (see Chapter 3). That is to say that the ASD group are motivated by painful and rewarding stimuli in a way that might be considered typical since they chose to negate pain in order to obtain a reward to the same degree as controls. Together, these results indicate that the absence or insensitivity to pain observed in the anecdotal accounts are not fully explained by either a peripheral nociceptive stimulus evoking a response, or a nociceptive stimulus initiating a motivational state to avoid it. That is to say, that the "wiring" of pain appears to be intact.

However, "pain" is complex (International Assosiation for the Study of Pain, 2020), it is not only the psychophysical experience of a noxious stimulus or the extent to which individuals are motivated by said noxious stimulus, but a personal experience that is communicated externally by pain behaviours (Craig, 2015). These pain behaviours are classified into verbal or non-verbal, such as rating how intense your pain is, or facially expressing your pain (Kunz et al., 2019). Both of which serve *a* purpose of communicating an otherwise subjective experience. This communication then holds social value and meaning, in that a person can communicate in order to seek help which potentially results in receiving care (Goubert et al., 2009; Hadjistavropoulos, et al., 2011; Yamada & Decety, 2009). In order for care to be provided, there must first be recognition by the observer or care

provider that what is being expressed is an experience of pain (Craig et al., 2001; Prkachin, 2009).

However, pain can be communicated with or without a social interaction such as help-seeking. Neonates and babies, who display clear signs of distress, shows the innate nature of pain communication (Craig et al., 1993; Fitzgerald, 1991), despite help seeking being a result of the communicated distress. Early vocalisations of pain by infants in the pre-speech period, highlight that pain-related sounds may exist as an involuntary expression, with social meaning attributed to these vocalisations through the behaviour of others that reinforce the meaning for the infant (Stanford et al., 2005; Stoel-Gammon, 2011). In adults, some vocalisations that are made when in pain, such as "ouch", can occur in isolation without the purpose of receiving care, with pain itself motivating people to communicate (Ferris et al., 2016). Few attempts have been made to explore the functionality of pain communication without the subsequent social meaning and interactions that are applied to them. One avenue considered swearing compared to neutral speech showing habitual swearing to have the greatest influence on reducing the magnitude of pain and increase the duration in which someone could keep their hand submerged in a cold pressor (Stephens et al., 2009; Stephens & Umland, 2011). Showing that expressing pain in verbal ways can act as a hypoalgesia (Swee & Schirmer, 2015). Additionally, the verbal interacts with the physical, in that vocalisations require the motor system to generate rib muscle movements to support phonation and articulation, the movement of which has been shown to modulate pain (Peretz & Gluck, 1999). The expression of pain, whether verbal or non-verbal may, therefore, not solely be for social communication. Rather, social meaning is applied as a result of an observable phenomena occurring as a result of pain itself, or of the attempt to alleviate the pain oneself.

A potential explanation to the apparent insensitivity to pain in ASD derives from a communicative perspective (Nader et al., 2004). Typically, individuals communicate pain using these aforementioned behaviours (Craig, 2009, 2015; Hadjistavropoulos, et al., 2011; Walsh et al., 2014), however, ASD, is characterised by striking impacts in expressive communication, including delayed, or total lack of language development (Oller et al., 2010). Therefore, it is likely that pain expression, particularly early vocalisations that develop as children age, is delayed or different. Furthermore, from a social-communicative perspective, these behaviours are developed in light of cultural norms, social values and sets of behaviours deemed most socially appropriate (Peacock & Patel, 2008; Schiefenhövel, 1995). Therefore, receptive social communication first must be intact to learn what is most socially relevant for expressive communication. Since ASD is further characterised by delayed receptive communication, discrepant comprehension of language (APA, 2013; Davidson & Ellis Weismer, 2017; Mitchell et al., 2006), as well poor eye contact (Corden et al., 2008; Pelphrey et al., 2002) and reduced social contagion (Beall et al., 2008; McIntosh et al., 2006; Wieckowski & White, 2017). It is likely that the ability to acquire expressive communication, or the ability to comprehend and utilise this effectively to provide the same social meaning is either reduced or different in ASD. The result of which is that signals being sent to an observer are lower in intensity or less clear and therefore observers may interpret the experience to be less, even if the experience itself is the same in ASD as it would be in those considered healthy.

Mercer and Glenn, (2004) were the first to investigate facial expressions in a group of DD children, showing that pain expression as measured by the Maximally Discriminative Facial Movement Coding System, was of a lesser intensity compared to controls. Importantly, the expressions observed were more complex in those with DD. With two adjacent areas tending to show pain, with another reflecting other emotions. These findings

indicate that expressions were much more blended in the developmentally delayed group, highlighting just how complex facial expression may be in those who are not-typically developing. Therefore, it may be unsurprising that observers have difficulty identifying pain in this group. However, these were infants who were not meeting their developmental milestones, not specifically those with an ASD diagnosis.

To investigate communication of pain in ASD, Nader et al., (2004), recorded children with and without ASD during venepuncture and coded the facial responses using the CFCS and the Observational Scale of Distress. Results showed similar general trend of increasing facial activity through baseline to post needle insertion for both groups. However, greater facial reactivity to venepuncture was present in the ASD group compared to controls. There was also greater behavioural distress regarding the procedure observed in the ASD group for post needle insertion and similar to the results observed by Tordjman et al., (2009), greater post procedural distress. However, it must be noted that procedures for the ASD and control group differed and that the purpose of venepuncture was different in the two groups, calling for caution when interpreting significant group differences. Despite this, results do indicate a significant observable reaction to a painful stimulus in ASD that is contradictory to that of other anecdotal evidence. Interestingly, Tordjman et al., (2009) also reported that 60.3% of autistic individuals displayed certain autistic behaviours following the venepuncture, including increased self-injurious behaviour, aggressive behaviours towards others and stereotyped behaviours. A paramount behavioural response reported was social withdrawal (38.1%). Findings allude to an autism specific atypical pain response, one that contradicts the typical help seeking that subsumes pain communication.

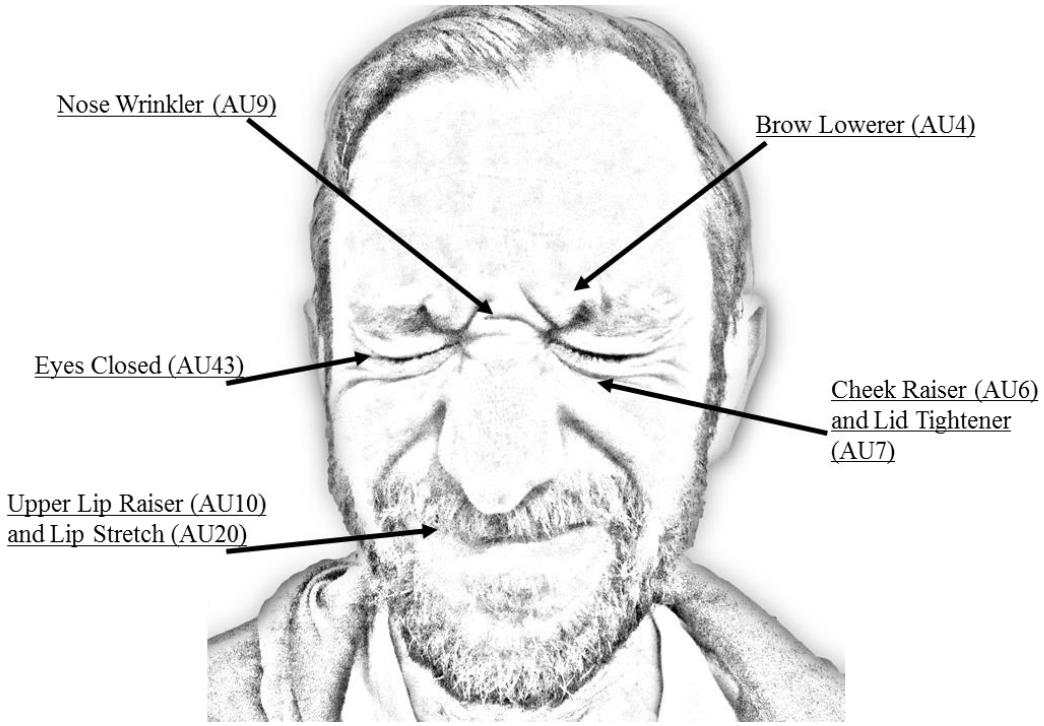
Rattaz et al., (2013) similarly investigated facial activity, behavioural responses, and physiological reactivity to venepuncture in children with and without ASD. Videos of the

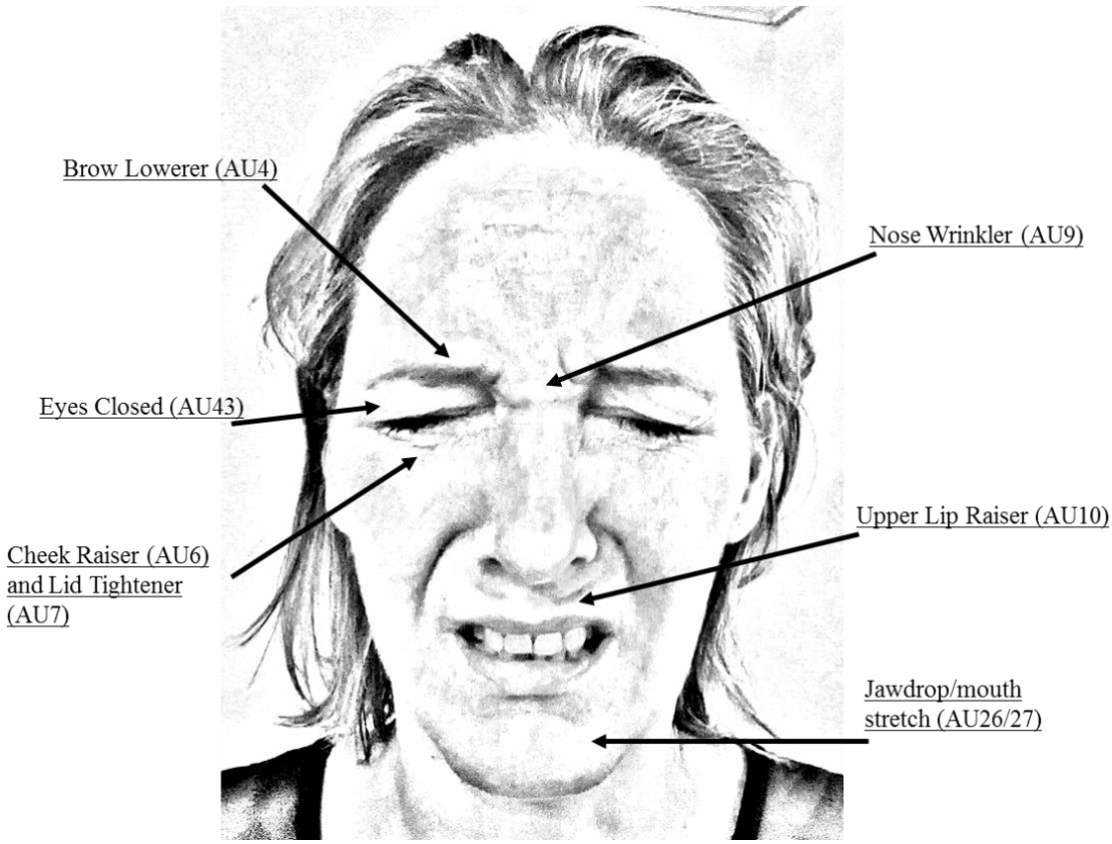
venepuncture were coded using the CFCS and the Grille d'Evaluation de la Douleur-Deficince Intellectuelle (GED-DI). Facial activity increased from baseline to venepuncture and a decrease thereafter for both groups. However, behavioural reactions as measured by the GED-DI remained high in the autistic individuals after the end of the venepuncture, in contrast to the comparison groups, supporting the results of Tordjman et al., (2009) and Nader et al., (2004). Taken together, these results suggest that autistic individuals could have a delayed recovery, or a delayed response to pain, which in turn supports the idea that painful procedures can lead to high levels of distress (physiological reactivity), even if such experiences are not conveyed in a manner that observers routinely recognise. However, these papers focus on facial reactivity as a composite of all facial action units that comprise the CFCS, rather than specifying the individual units which are observed during pain.

The CFCS is an adaption of the FACS, which is a more comprehensive system, in that there are more facial expressions and more combinations of facial expressions than in the CFCS (Breau et al., 2001). There are specific action units (see figure 17), as defined by the FACS (a precise measurement technique) that comprise a painful expression. These action units include Brow Lowerer (AU4), Cheek Raiser (AU6), Lid Tightener (AU7), Nose Wrinkler (AU9), Upper Lip Raiser (AU10), Lip Stretch (AU20), Jaw drop/mouth stretch (AU26/27), Eyes Closed (AU43) and Blinking (AU45; Craig et al., 1991; LeResche, 1982; LeResche & Dworkin, 1988; Patrick et al., 1986; Prkachin, 1992; Prkachin & Mercer, 1989).

Figure 17.

Facial Action Units (AU's) identified in the research as being related to pain





Note. Facial Actions units (AUs) of the upper and lower face in relation to pain. These are for diagram purposes only and are not participants. These are actors. All images belong to the author of this thesis, having been photographed, edited, and adapted by the author (SV) for the purposes of generating this diagram.

More experimentally robust research, which investigated painful expressions across different types of stimulus modalities namely temperature, pressure, electrical and ischemia, showed that only four of these facial actions are more steadily displayed for pain stimuli. These were the Brow Lowerer (AU4), Lid Tightener (AU7) and Eyes Closed (AU43), Nose Wrinkler (AU9) and Upper Lip Raiser (AU10). Each of these units showed increasing likelihood of occurring across all pain modalities as well as increases in intensity and duration (see figure 17). Further work, establishing differences in units displayed in clinical and experimental settings has highlighted an overlap in these action units. Therefore, these units are thought to be the universal key components of the facial expression of pain, that is distinguishable from non-noxious emotional states (Kunz et al., 2019; Simon et al., 2008). Importantly, this work is largely reliant on typically developing individuals, or those considered otherwise healthy who may be in a clinical state of pain. Little of the work exploring the nature of FACS units, which are indicative of pain, has been conducted when considering different diagnoses and in particular individuals with altered social communication. Undermining the universality of these units to all groups of individuals. Furthermore, the studies on ASD (Nader et al., 2004), use these pain facial units as a global standard of pain expression in order to identify pain in this population reporting only the gross number of units shown, rather than seeking specific units that may be associated with pain in ASD. Without this same basic work establishing which units comprise a painful expression in ASD, it is difficult to determine if the same units are used in the same way to express pain in this population. Additionally, these expressions are socially predicated, and so when considering a group of individuals whose diagnoses is characterised by social impairment it is plausible that these expressions are different in either the type, intensity, or duration. This could lead observers to different inferences about the pain, such as the insensitivity discussed in anecdotal accounts.

The findings from the previous studies show that there may be increased facial activity during potentially painful or distressing experiences, but with little specificity for the units that comprise the expressions. Autistic individuals also showed greater self-soothing and behavioural reactions that lasted into the recovery period raising questions about an autism specific response to pain (Nader et al., 2004; Rattaz et al., 2013; Tordjman et al., 2009) that is contrary to what we know about pain in typically developing individuals. However, each of these studies not only used a predefined expression of pain based on very socially different individuals, but they were all conducted in children who were verbally unable to communicate their pain. Pain is inherently a subjective experience; therefore, it is important to be able to match painful facial expressions to verbal reports of pain. Particularly if we are then to attempt to delineate what a painful expression in autism may look like. The limited research to date also highlights that not enough is known about the pain experiences of autistic individuals (Nader et al., 2004; Rattaz et al., 2013; Tordjman et al., 2009). Research is required to inform how and why deficits occur and uncover alternative or atypical pain responses. Further, all studies to date have been conducted with children and therefore nothing is known about facial expressions of pain or pain behaviours in adults with ASD.

Non-verbal expressions of emotion such as facial activity, may be less amenable to conscious distortion than that of self-reports and subjective states, therefore providing a more objective way to measure pain with a reduction in the likelihood of a misrepresentation of pain experience (Patrick et al., 1986). Knowing a participant is experiencing pain, and then investigating the expressions associated with that pain can help establish the same basic units as reported for typically developing individuals. The aim of this project is therefore to utilise the Facial Action Coding System, alongside the Non-Communicating Adults Pain Checklist (NCAPC), to code facial and behavioural responses to pain which can be confirmed as being associated to pain via pain intensity ratings. To ensure that nuances in expressions are

considered it will also take the approach of coding individual action units rather than the composite scores of facial reactivity previously utilised. Additionally, participants will be communicating adults with autism able to self-report the intensity of the stimulus. Previous research has been largely reliant on clinical pain states and failed to determine whether these expressions were consistent for different types of pain therefore, the current experiment will be conducted in a lab using controlled painful stimuli that is both tonic and phasic. It is hypothesised that the ASD group will show differing facial activity and behavioural responses to increasing hot and cold temperatures, and that these facial expressions will differ in terms of frequency of occurrence as well as intensity compared to controls.

4.2 Methods

4.2.1 Participants

Sixteen adults (14 males) who had not participated in Experiments 1 and 2, aged between 18 and 59 years were recruited (M = 25.13, SD = 12.23). Eight ASD participants (7 males and 1 female) with a mean age of 24.38 years (SD = 4.13) were recruited via the university's participant panel, who had a diagnosis from a specialist diagnostic service within a local hospital trust and had received their diagnosis based on the DISCO and/or ADOS from a trained clinician. Diagnostic letters were obtained from participants, which confirmed diagnosis and IQ values >70, additionally, educational level was taken as a proxy measure. Participants were screened for inclusion using a health questionnaire. Those suffering from severe facial disfigurements, major motor deficits, chronic pain, diabetes, Raynaud's syndrome, eczema, or sensitive/broken skin were excluded. Additionally, participants were asked specifically about any history of a severe psychiatric disorder and were excluded if present. The difference in gender split across autism is not unexpected as ASD is strongly biased towards males (Lyall et al., 2017).

Eight participants without an autism diagnosis were recruited through advertisement, selected to match each individual with autism on age: within a limit of ±5 years (M = 25.88, SD = 4.78) and gender (7 males, 1 females). All were subject to the same exclusion/inclusion criterion described above, with the addition of SIB i.e., self-cutting. This was only applied to the individuals without autism because for autistic individuals, SIB tends to be classified as "stereotyped SIB" as opposed to the "impulsive SIB" that is habitual in nature and generally observed in individuals with a serious psychiatric illness (e.g., self-mutilation) or typically developing adolescents and adults (e.g., self-cutting; Minshawi et al., 2014; Yates, 2004). Furthermore, the nature of SIB in autism is a behaviour of interest, therefore a comparison to individuals without SIB, especially and SIB that is phenotypically and psychiatrically different is essential. Although they were not explicitly matched on IQ, the control group were from the general population, suggesting IQ>70 and educational level was taken as a proxy measure for IQ. All participants in both groups were without pain medication or alcohol at least 24 hours before the investigation.

As groups (n = 8 per group) were age and gender matched they did not significantly differ; U = 39.000, z = .740, p = .505, and $\chi^2(1) = 0$, p = .767 respectively. As expected, groups had significantly different AQ scores, U = .000, z = -3.391, p = .000, with the autism group scoring higher (see table 15 for descriptive statistics).

Table 16:

Characteristics and questionnaire results of ASD and control group

Characteristic		ASD	Controls	Total
No. of participants		8	8	16
No. of participants with	ASD	3	-	3
	Asperger's	5	-	5
Age		24.38 (11.67)	25.88 (13.53)	25.13 (12.23)
Gender Female		1	1	2
Male		7	7	14
Autism Quotient (AQ)*		34.50 (6.19)	16.25 (5.92)	25.38 (11.09)

Note. All values are given as mean (*SD*). *p<.05. ASD (Autism Spectrum Disorders).

The experiment was approved by Liverpool John Moores Ethics Committee (REC ref: 15/NSO/054) and all participants gave written informed consent. Participants received information both orally and in writing that painful stimuli would be administered.

4.2.2 Questionnaires

All questionnaires were completed by both groups. The AQ was used to quantify autistic trait severity, meanwhile the RBS-R and TAS-20 were used to measure symptomology associated with ASD. The PCS and FP to gain a measure of pain catastrophizing and fear of pain, for descriptive purposes. An additional scale was used to measure Kinesiophobia; TSK. All the aforementioned scales are described in previous Chapters 2 and 3 (see sections 2A..2.2.1.1 for AQ, 2A.2.2.1.2 for PCS, 3.2.3.1.1 for FP, 3.2.3.1.2 for RBS-R, 3.2.3.1.3 for TAS-20 and 3.2.3.1.4 for TSK).

4.2.3 Psychophysical Responses

4.2.3.1 Determination of Heat Pain Threshold and Tolerance

Prior to the experiment, heat pain threshold (HPT) was measured using the method of limits protocol described in Chapter 2, section 2A.2.2.2.1. Alongside this a measure of HTOL was also obtained. In brief this followed a similar protocol to the HPT; a thermode was heated at 1°C/second until participants pressed a button to indicate they had reached a

point at which the painful temperature could no longer be tolerated. This was to ensure there were no differences in peripheral temperature processing that may account for differences in outcomes of the experiment.

4.2.3.2 Determination of Cold Pressor Threshold and Tolerance

Cold pain threshold and tolerance was measured using the same procedure described in Chapter 2 section 2A.2.2.3.2, where participants submerged their hand in 3°C water. The chosen temperature allowed submersion for a duration of 10 seconds or greater (Mitchell et al., 2004). Since the Cold Pressor test induces pronounced sympathetic activation and vasoconstriction, the maximum duration of limb immersion was set at three minutes (Mitchell et al., 2004). In brief, the threshold was determined as the time (in seconds) to which a participant indicated that the temperature was painful, and tolerance was the time (in seconds) at which the participant removed their hand.

4.2.3.3 Data analysis and preparation for Heat and Cold Pain Threshold and Tolerance

For HPT and HTOL a mean value of three measures was taken. For HPT the data evaluation process discussed in Chapter 2 section 2A.2.4 was followed to create a *Z*-score value. This was to enable comparison to published norms to ensure that the sample had typical heat pain processing. For HTOL mean values were compared across groups to ensure no significant differences were present. *T*-tests were used to determine group differences, or where assumptions were violated Mann-Whitney *U* (note: data for Cold Pressor required no such data preparation and so *t*-tests or Mann-Whitney *U* tests were also used to test group differences).

4.2.4 Facial Expression Responses

4.2.4.1 Stimulus for Facial Responses to Non-Painful and Painful Heat Stimuli

4.2.4.1.1 Heat Stimulus

Phasic heat stimuli were delivered by a Medoc Pathway Advanced Thermal Stimulator to determine response to increasing heat stimuli. A CHEPS thermode, attached to the dorsal side of the dominant hand, was heated from a baseline temperature of 38°C, at a ramp rate of 4°C/sec until its target temperature. Once the target temperature was reached the stimulus remained at the maximal plateau for five seconds before returning to the baseline at a rate of 4°C/sec. Long interstimulus intervals were used to prevent sensitisation (15-20seconds) and to allow enough time for participants to rate the stimulus intensity. Target temperatures were set at 41°C (non-painful), 44°C (moderately painful) and 47°C (very painful). Participants received 18 thermal stimulations in total (six of each intensity) in a random order produced by the Pathway Stimulator.

4.2.4.1.2 Cold Stimulus

The psychophysical measurement of cold pain threshold and tolerance was used as the cold stimulus for recording facial responses. Participants kept their hand submerged in the 3°C water and were instructed to remove their hand when they could no longer tolerate the pain.

4.2.4.2 Assessment of Facial and Behavioural Responses to Non-Painful and Painful Heat Stimuli

4.2.4.2.1 Video Recordings

Participants were recorded for the duration of the experiment with a Go Pro Hero 5 camera in high definition (1080p), that was positioned facing them at 2m away and set at eye

level for each participant to ensure the face was clearly recorded. An LED visible to the camera but not to participants was lit concurrently with thermal stimuli (during the plateau of maximal temperature) to mark on-sets of stimulation. Adobe Premier Pro (Adobe®) was used to segment the videos into 5 second segments beginning just after the stimulus had reached the target temperature except for the cold pressor tolerance, which was taken five seconds prior to removal. In total, 18 segments were produced for scoring for heat pain stimulation and three for cold pain stimulation; one for when the hand was first submerged, one when the stimulus became painful and one for just prior to hand removal signifying tolerance. Videos were then exported into their frames at a rate of 30fps. These frames were then used to analyse facial expressions (n = 150 frames per stimulus [5 second clip]).

4.2.4.2.2 Facial Expressions of Pain

Facial responses were quantified using the FACS (Ekman, 1992), a system considered the gold standard for assessing facial expression which can be applied to video, frame by frame or individual images. The FACS is an objective system, which is anatomically based and permits exhaustive descriptions of the basic units of facial movement constituting an expression or series of expressions. The FACS manual, trains an individual to detect appropriate units and their intensity. By using the manual to work through the 63 individual actions, 28 action units, 13 action descriptors, 11 movement codes, eight gross behaviours and 14 head and eye units, complex facial expressions can be scored. A trained coder (the researcher) identified the presence or absence and intensity of actions for each frame. Each action was scored on an intensity scale from A(Trace) to E(Maximum). In order to allow for quantitative analysis, the intensity scale was converted to a numerical equivalent where 1 was trace, and 5 was maximum. There were two exceptions to this: the AU0 (neutral) and the AU45 (blink), due to the nature of the criteria for each of these as being solely either present

or absent. Each frame was scored using the FACS 16 step process (see table 16 for broad overview).

Table 17:

FACS procedure for scoring facial expressions adapted from Ekman, Friesen, & Hager (2002).

Step	Action
Step 1	Initial scoring of the Lower Face – checking which AU's are present and which intensity
Step 2	Check for omissions - AUs not considered
Step 3	Reorganise the initial scoring based on Step 2
Step 4	Check alternative AUs and reference sections for combinations and intensity rating
Step 5	Verify intensity criteria, unilaterality and Top/Bottom Lip
Step 6	Final decisions on AUs
Step 7	Record the final scoring
Step 8	Re-check reference sections and contraindications
Step 9	Score Head and Eye instructions
Step 10	Head/Eye Check in lieu of scoring Head and Eye Positions
Step 11	Applicability of the Head and Eye Positions (i.e., if scoring images there are certain rules)
Step 12	Score Head Positions
Step 13	Score Eye Positions
Step 14	Integrate Head and Eye Position Scores
Step 15	Enter Head and Eye scores
Step 16	Now return to step one and complete for Upper Units.

Note. AU = Action Unit and AD = Action Descriptor.

4.2.4.3 Data Preparation and Analysis of Facial Expression of Pain for Cold and Thermal Stimuli

Following coding of all FACS data, the data was simplified to remove those actions that never occurred in the entire sample. There was one action unit, seven action descriptors,

six gross behaviours, and one eye position that did not occur, including all 10 movement codes which could not be applied to individual frames (see Appendix D). These were all removed from subsequent preparation and analysis.

Each intensity rating for a frame was initially transformed into a new present or absent variable (1 present, 0 absent) to allow for a global presence or absence score of each action in each stimulus and to also allow for a frequency to be calculated. For every stimulus therefore, whether an action unit was observed to be present at any timepoint in the presentation of the stimulus was noted, as well as frequency (n/150 images). Frequency meaning the maximal presence of an action unit observed for the duration of the stimulus.

For every stimulus, a sum-total score was also generated for each action by summing the intensity rating for all 150 frames. A maximal intensity score of 750 was achievable if all 150 frames were coded at 5. Furthermore, presence/absence, frequency and sum-total scores were calculated for clusters. For both frequency and sum-total, the mean value of its constituent actions was calculated. Table 17 shows which action units comprised which clusters.

Table 18:

Clusters and their respective action units and descriptors

Cluster	Unit Number	Unit Description
Upper	AU4	Brow Lowerer
	AU1	Inner Brow Raiser
	AU2	Outer Brow Raiser
	AU5	Upper Lid Raiser
	AU7	Lid Tightener
	AU6	Cheek Raiser and Lid Compressor
	AU43	Eye Closure
	AU45	Blink
	AU46	Wink
Lower Vertical	AU9	Nose Wrinkler
	AU10	Upper Lip raiser
	AU17	Chin Raiser
	AU15	Lip Corner Depressor
	AU25	Lip Part
	AU26	Jaw Drop
	AU27	Mouth Stretch
	AU16	Lower Lip Depressor
Lower Horizontal	AU20	Lip Stretch
	AU14	Dimpler
Lower Oblique	AU11	Nasolabial Furrow Deepener
	AU12	Lip Corner Puller
	AU13	Sharp Lip Puller
Lower Orbital	AU18	Lip Pucker
	AU22	Lip Funneler
	AU23	Lip Tightener
	AU24	Lip Pressor
	AU28	Lip Suck
Miscellaneous	AU8+25	Lip Towards Each Other
	AD19	Tongue Show
	AU31	Jaw Clencher
	AD32	Lip Bite
	AU38	Nostril Dilator
	AU39	Nostril Compressor
Head	51	Head Left
	52	Head Right
	53	Head Up
	54	Head Down
	55	Head Tilt Left
	56	Head Tilt Right
	57	Head Forward
	58	Head Back
Eyes	61	Eyes Left
	62	Eyes Right
	63	Eyes Up
	64	Eyes Down
	65	Wall Eye
Gross Behaviour	82	Shoulder Shrug
	91	Flash
	92	Partial Flash

Note. AU = Action Unit and AD = Action Descriptor.

To select those actions that were present during pain in the present context, actions had to occur in >5% of the painful segments for the entire sample. Actions that were not present in the sample for the cold stimulus (i.e., sensation, pain, and tolerance) were excluded from the analysis (see Appendix E). For thermal stimulation all action units mentioned above (see table 17) were included. Chi-squared analysis was conducted to determine group differences in the presence of an action unit for each stimulus presented across clusters. *T*-tests were used to determine group differences between cold stimuli facial expressions, or where assumptions were violated Mann-Whitney *U* was used. Nine (one for each cluster) 2* (Group [ASD/controls]) *3 (Thermal Stimuli Strength [no-pain/moderately painful/painful]) mixed ANOVAs were run to determine group differences in the facial expressions of pain across thermal stimuli strengths. Follow-up tests included running the same analysis protocol on individual action units and additional units.

4.2.5 Behaviour

4.2.5.1 Behavioural Expressions of Pain

NCAPC is a revised pain measurement tool of the NCCPC, designed specifically for adults with intellectual disability. It includes the subscales; vocal reaction, emotional reaction, facial expression, body language, protective reaction and physiological reaction. There are 17 specific behaviours to be rated on a 4-point Likert Scale, ranging from 0 (Not observed at all) to 3 (Observed very often). Total scores range from 0 (no pain observed) to 51 (maximal duration of all pain behaviours observed). Therefore, a greater score means greater pain. Using this measure two independent raters assessed the extent to which each participant displayed the pain behaviours across the duration of the entire experiment.

4.2.5.2 Data Preparation and Analysis of Behavioural responses using the NCAPC

Coding using the NCAPC was a fully crossed design where both raters coded all participants. Total NCAPC scores were computed for each rater and used in Inter-Rater Reliability (IRR) analysis. IRR was assessed using a two-way mixed, consistency, average measures Interclass Correlation (ICC), to determine the degree to which raters provided consistency in their ratings of observed pain behaviours as measured by the NCAPC. The resulting ICC showed moderate reliability, indicating agreement, therefore pain was rated moderately similar across the raters, *ICC* = .750 for the ASD group. However, there was less agreement in raters for the control group, *ICC* =.227. There was, therefore, some measurement error introduced by raters in terms of the control group. Therefore, for further analysis of behavioural differences between groups, a mean overall score for each participant was created using both the raters scores for each item. *T*-tests were conducted to establish group differences in observed pain behaviours. All analyses were conducted using SPSS version 23.

4.2.6 Self-report Pain Ratings

Participants were asked to evaluate the thermal stimuli above in two ways. Firstly, participants indicated whether the stimulus was painful or not. Secondly, they rated the unpleasantness and then the intensity of the stimulus on a 10-point Likert scale; 0 (not unpleasant/intense) to 10 (extremely unpleasant/intense). Participants did this at the beginning and then the end of the experiment for thermal stimuli.

4.2.6.1 Data Preparation and Analysis of Self-reported Ratings of Heat Stimuli

A mean rating was created for both pain intensity and unpleasantness from the initial rating and the rating at the end of the experiment. Fishers exact test was conducted on

whether participants found the stimulus to be painful or not, and *t*-tests, or Mann-Whitney *U* tests were assumptions were violated were used to determine group differences in pain intensity and unpleasantness.

4.2.7 Procedure

All participants gave informed consent after being briefed and completed the health screening as well as the AQ, RBS-R, PCS and FP online prior to attending the laboratory for the experiment. The laboratory session lasted 20 minutes, during which the participant sat upright in a comfortable chair facing the camera. Participant's faces were recorded throughout the procedure. Participants were asked to keep interaction to a minimum, only answer the questions asked (unless they wanted to cease participation), and to focus on a letter 'H' placed just behind the camera. The testing procedure included the assessment of pain sensitivity (pain threshold and tolerance) to heat and cold stimuli, the assessment of facial and subjective responses to cold stimuli first followed by nonpainful, moderately painful and very painful heat stimuli. Pain was induced experimentally in the ways discussed above (see sections 4.2.4.1.1 and 4.2.4.1.2). Lastly, participants completed an alexithymia scale.

4.3. Results

KS tests revealed that restrictive behaviour patterns were not-normally distributed therefore non-parametric tests were conducted (ASD: $KS(8) = .152$, $p = .200$, Controls: $KS(8) = .422$, $p = .000$). These revealed that the ASD group experienced significantly greater restrictive repetitive behaviour patterns $U = 2.000$, $z = -3.155$, $p = .001$, $r = -.79$ (RBS-R Lam & Aman, (2007)) that were rated as having a greater impact on daily functioning $t(11) = 6.856$, $p = .000$, $\delta = 3.61$. The ASD group also experienced greater levels of alexithymia $t(11)$

= 4.657, p = .000, δ = 2.33 compared to controls (see table 18). These findings are consistent with previous investigations and what is known about autism symptomology.

Table 19:

Descriptive statistics for Questionnaire results for both ASD and Control groups

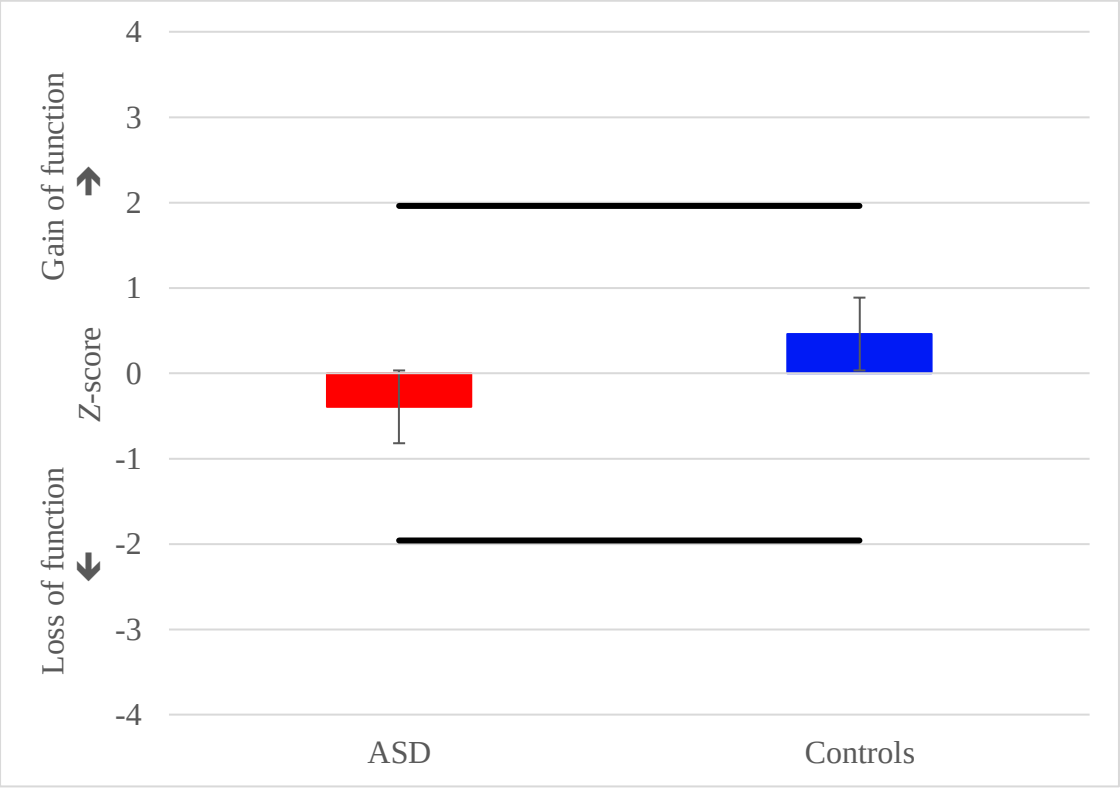
Characteristic	ASD	Controls	Total
No. of Participants	8	8	16
Pain Catastrophizing scale (PCS)	20.50 (16.27)	12.50 (9.49)	16.50 (13.52)
Fear of Pain Questionnaire (FP)	85.50 (26.63)	76.63 (27.52)	81.06 (26.56)
Restrictive Repetitive Behaviour Scale (RRBS)*	41.38 (18.84)	8.13 (9.46)	24.75 (22.41)
RRBS Global Rating*	53.63 (14.27)	13.40 (6.69)	38.15 (23.42)
Toronto Alexithymia Scale (TAS-20)*	61.88 (8.48)	43.75 (7.03)	52.81 (2.01)

Note: All values given and mean (*SD*). *p<.001. ASD (Autism Spectrum Disorder).

4.3.1 Heat Pain Thresholds and Tolerance

Figure 18.

Adjusted Z-scored Heat Pain Thresholds for the ASD and Control group



Note. Adjusted Z-score data for ASD vs. control group for HPT including standard error bars. Any column that extends outside the 95% confidence interval of the normal distribution of healthy subjects (=area between the black lines) signifies sensory changes.

T-tests revealed that there were no significant group differences (see figure 18) in heat pain threshold or heat pain tolerance levels (see table 19) indicating typical psychophysical response $t(14) = -.865$, $p = .402$, $\delta = .43$ and $t(14) = -1.310$, $p = .211$, $\delta = .65$, respectively. These findings support those of earlier studies, therefore any difference in the expression of pain for thermal stimuli in this experiment are unlikely a result of altered sensory processing (Fründt et al., 2017; Vaughan et al., 2019).

Table 20:

Untransformed data values (given in ◦C) of QST Heat Pain Threshold and Heat Pain Tolerance for ASD and Control groups

	ASD	**Controls**	***p* value**	**Effect size (δ)**
Heat Pain Threshold (HPT; ◦C)	43.76 (4.92)	45.98 (3.28)	.402	.43
Heat Pain Tolerance (HPT; ◦C)	48.38 (2.72)	49.91 (1.91)	.211	.65

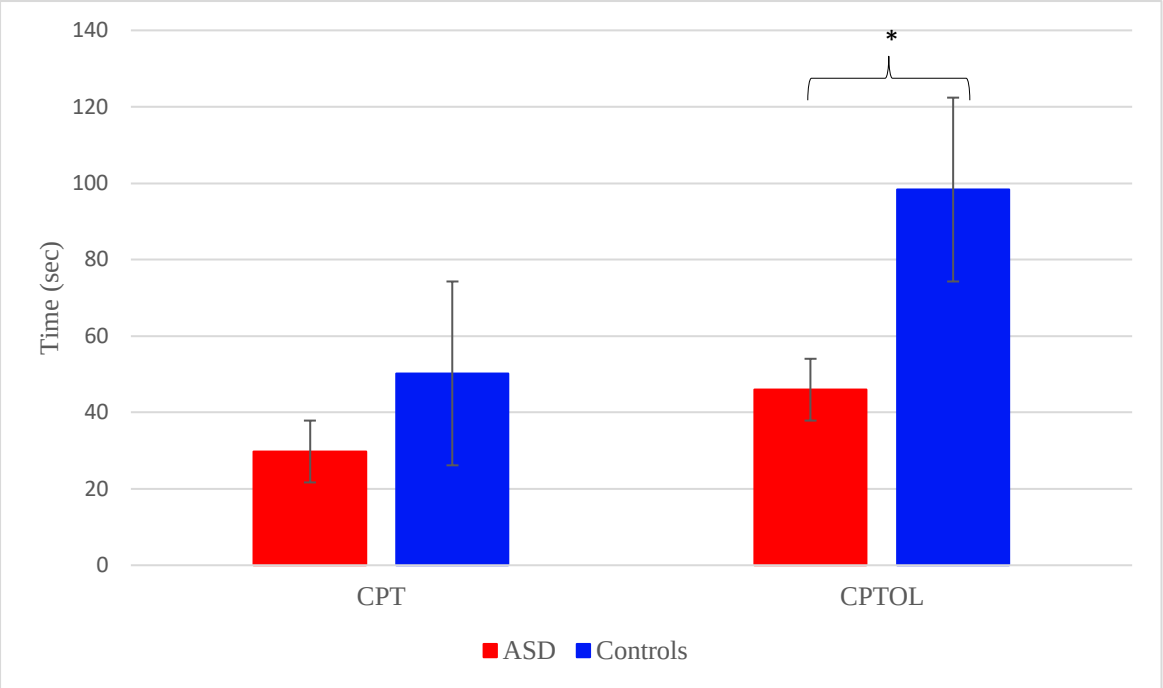
Note: Group raw data values for each QST parameter and additional sensory tests given as mean (*SD*) to aid understanding in terms of their actual unit of measurement i.e., temperature in Celsius.
All *p* values and effect sizes given for HPT are for the inferential statistics conducted on transformed data as discussed in Chapter 2.

4.3.2 Cold pressor Threshold and Tolerance

Mann-Whitney *U* tests revealed that there were no significant group differences in cold pressor threshold (CPT) indicating typical psychophysical response, $U = 42.000$, $z = 1.050$, $p = .328$, $r = .26$. However, they revealed that the ASD group had significantly lower cold pressor tolerance (CPTOL) than controls, $U = 55.000$, $z = 2.415$, $p = .015$, $r = .61$ (see figure 19), therefore, for the ASD group, any differences in facial expressions of pain in relation to cold pressor tolerance could be related to a greater sensitivity that results in poorer tolerance of cold temperatures. This data contrasts with Experiment 2 which showed no differences in cold pressor threshold and tolerance. This variability in outcome is likely to reflect the heterogeneity in responses in autism, which is discussed later.

Figure 19.

Cold Pressor Threshold and Tolerance values (seconds) for both ASD and Control groups



Note. Raw values given as mean and standard error (*SE*) seconds for both cold pressor threshold (CPT) and tolerance (CPTOL) for ASD and control group. *p <.05.

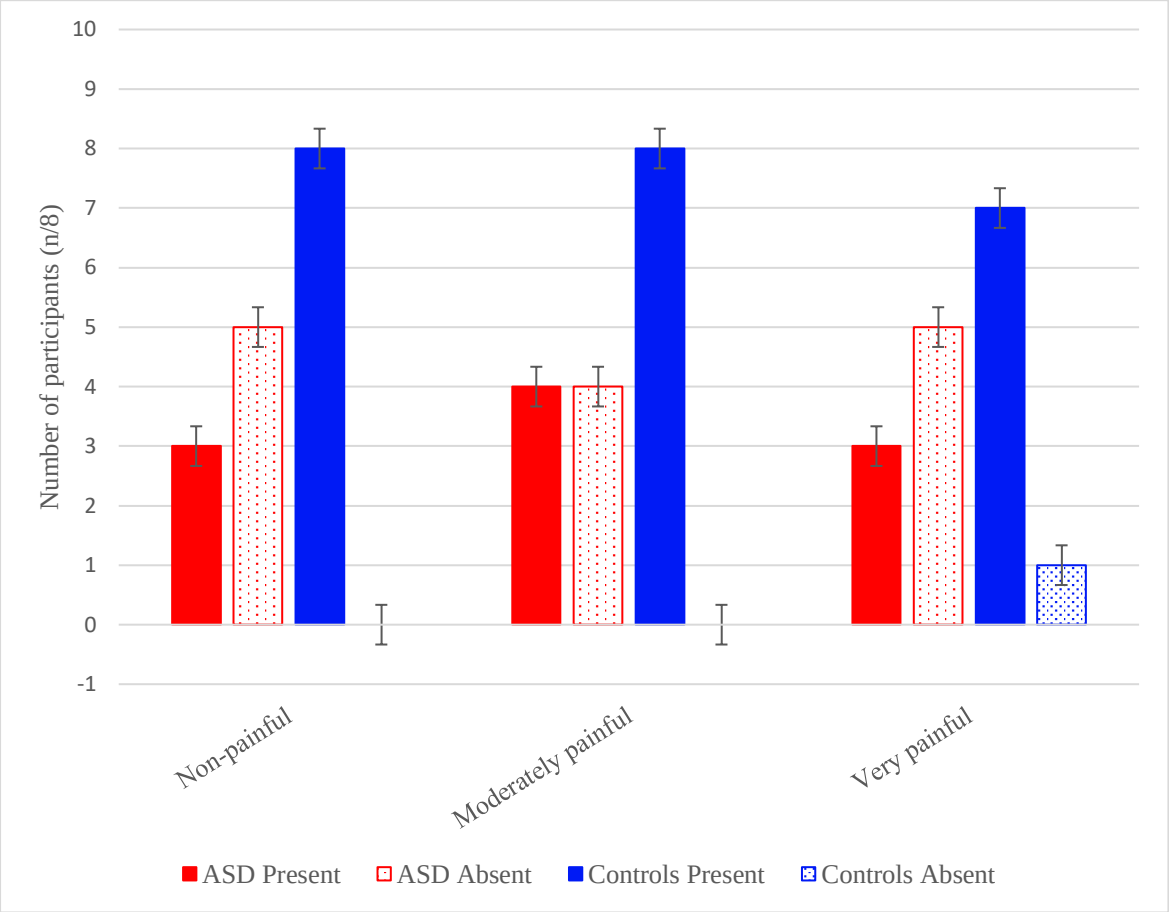
4.3.3 Facial Expressions of Pain to Thermal Stimuli (Heat)

4.3.3.1 Present/Absent data for Thermal Stimuli (Heat)

As the expected count assumption was not met, Fisher's exact test is reported for all clusters (see table 20). The control group showed a significantly greater presence of Neutral expressions for non-painful (p = .013) and moderately painful thermal stimuli (p = .038), with a trend towards significance in very painful thermal stimuli (p = .059), compared to ASD group (see figure 20).

Figure 20.

Number of participants (n/8) showing the Neutral (AU0) expression for Non-painful (41°C), Moderately painful (44°C), and Very painful stimuli (47°C)



Note. Raw values given as mean and standard error (*SE*) number of participants in each group, for each stimulus strength.

During non-painful thermal stimuli, Fisher's exact *t*-test showed that ASD participants were more likely to make facial expressions using the Lower Orbital cluster (p = .005). For moderately painful thermal stimuli, the ASD group moved their eyes more frequently than controls (p = .020). There were no other group differences in clusters, particularly for very painful thermal stimuli (p >.05), therefore facial expressions, at least in terms of them being present during painful thermal stimuli, are similar in the ASD group and controls.

Table 21:

Fishers exact tests for all clusters for Thermal Stimuli

Cluster	**ASD (*n*)**		**Controls (*n*)**		***p value***	***Odds ratio***
Non-painful (41°C)	Present	Absent	Present	Absent		
Neutral (AU0)*	3	5	8	0	.013	.375
Upper	8	-	8	-	-	-
Lower Vertical	7	1	4	4	.141	.143
Lower Horizontal	2	6	1	7	.500	.429
Lower Oblique	7	1	3	5	.059	.086
Lower Orbital*	7	1	1	7	.005	.020
Misc.	1	7	1	7	.767	1.000
Head	7	1	3	5	.059	.086
Eyes	6	2	2	6	.066	.111
Gross Behaviour	2	6	1	7	.500	.429
Moderately painful (44°C)						
Neutral (AU0)*	4	4	8	-	.038	.500
Upper	8	-	8	-	-	-
Lower Vertical	6	2	5	3	.500	.556
Lower Horizontal	1	7	1	7	.767	1.000
Lower Oblique	6	2	4	4	.304	.333
Lower Orbital	6	2	2	6	.066	.111
Misc.	3	5	-	8	.100	.625
Head	7	1	3	5	.059	.086
Eyes*	7	1	2	6	.020	.048
Gross Behaviour	3	5	1	7	.285	.238
Very Painful (47°C)						
Neutral (AU0)	3	5	7	1	.059	11.667
Upper	8	-	8	-	-	-
Lower Vertical	7	1	5	3	.285	.238
Lower Horizontal	3	5	-	8	.100	.625
Lower Oblique	7	1	4	4	.141	.143
Lower Orbital	7	1	4	4	.141	.143
Misc.	2	6	1	7	.500	.429
Head	6	2	3	5	.157	.200
Eyes	5	3	3	5	.310	.360
Gross Behaviour	4	4	1	7	.141	.143

Note: All values given as *n* = number of participants. * = significant relationships found ($p<.05$).

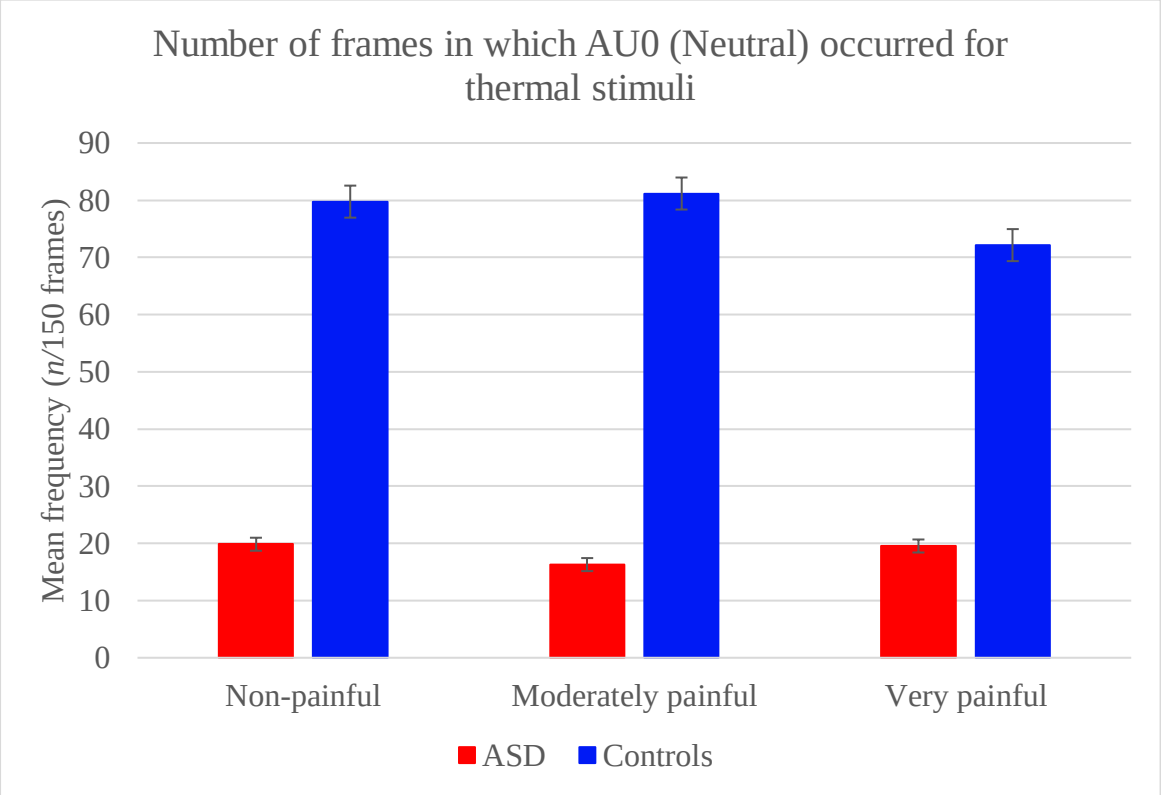
4.3.3.2 Frequency Data for Thermal Stimuli (Heat)

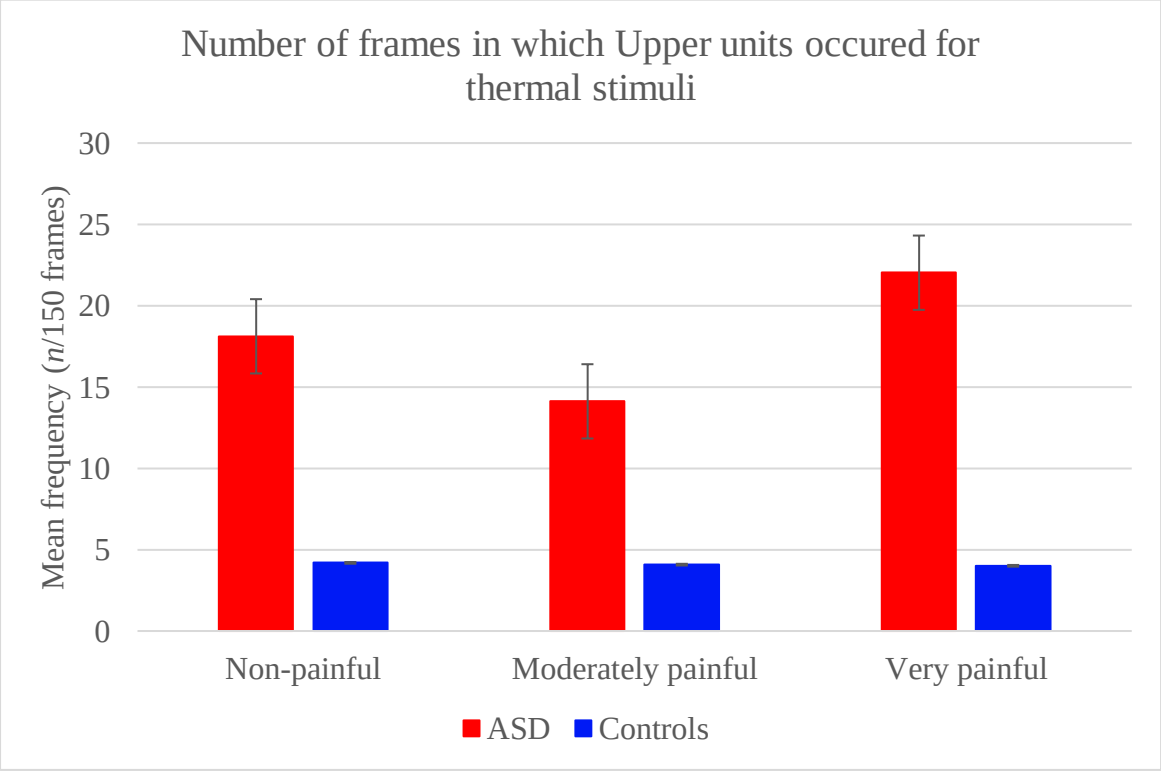
A series of 2 (Group [ASD/Controls]) *3 (Stimulus strength [non-painful/moderately painful/very painful]) mixed ANOVAs were run to determine group differences in clusters at different stimuli intensities. They revealed a significant main effect of group, for AU0 (Neutral; $F(1,14) = 7.210$, $p = .018$, $\eta_p^2 = .340$), Upper ($F(1,14) = 14.137$, $p = .002$, $\eta_p^2 = .502$), Lower Orbital ($F(1,14) = 16.793$, $p = .001$, $\eta_p^2 = .545$), and Head ($F(1,14) = 10.026$, $p = .007$, $\eta_p^2 = .417$) clusters, wherein the ASD group had greater frequency of facial

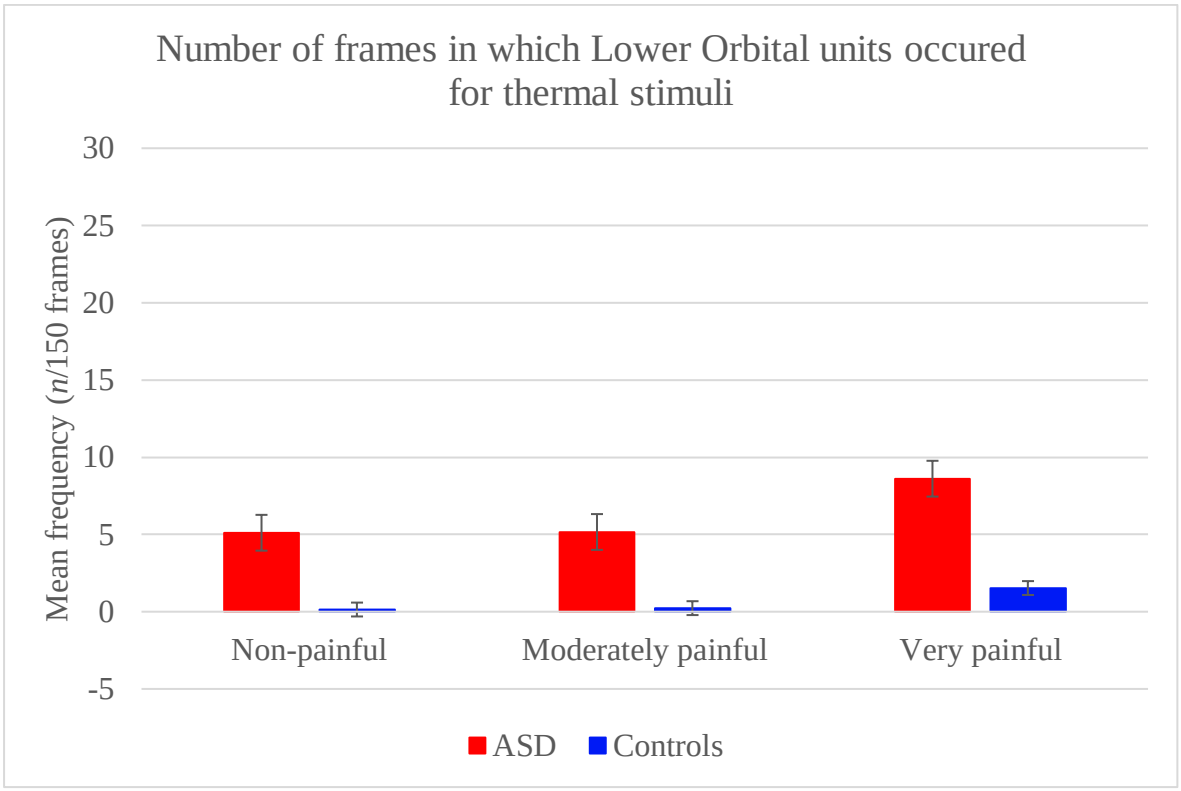
expressions at every level of thermal stimuli (see figure 21). For, AU0 the ASD group showed more expression throughout the experiment regardless of stimuli intensity, whereas controls showed more Neutral expressions except for very painful where more expression occurred.

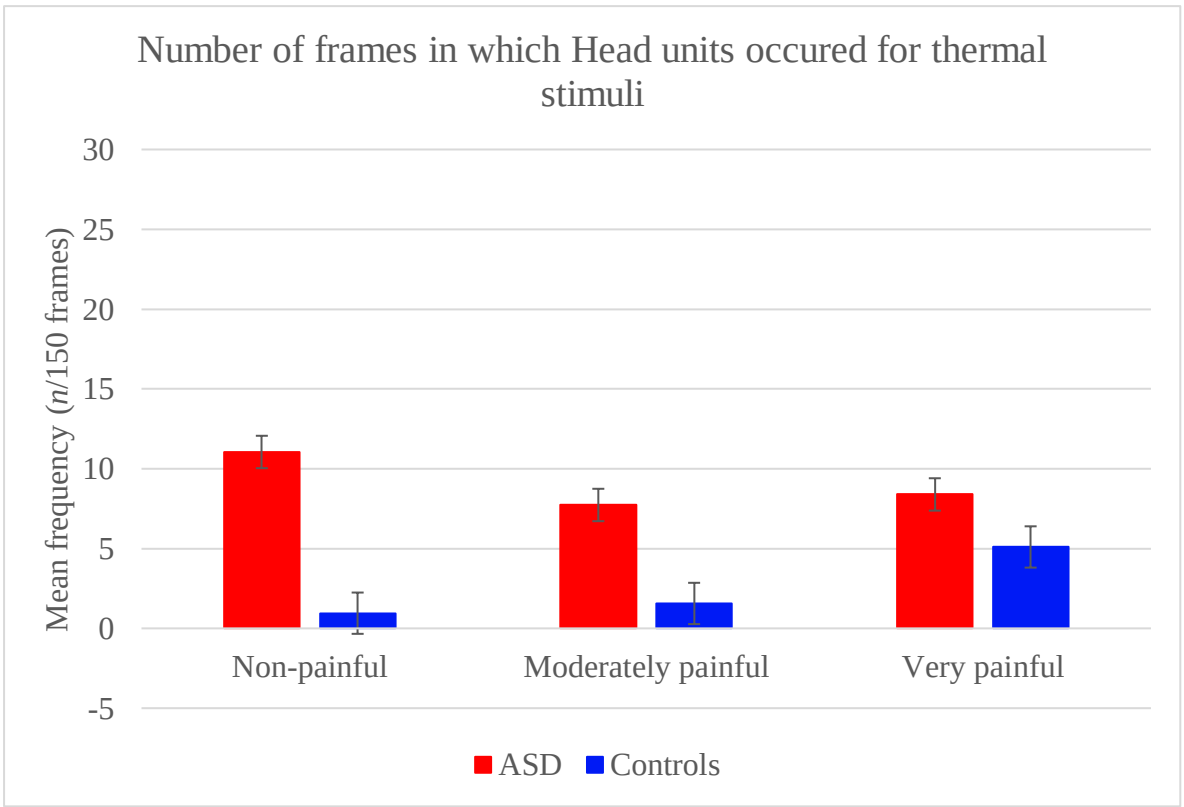
Figure 21.

Demonstrates the frequency (n/150 frame) that clusters occurred for Non-painful (41°C), Moderately painful (44°C), and Very-Painful heat stimuli (47°C) for ASD and Control groups







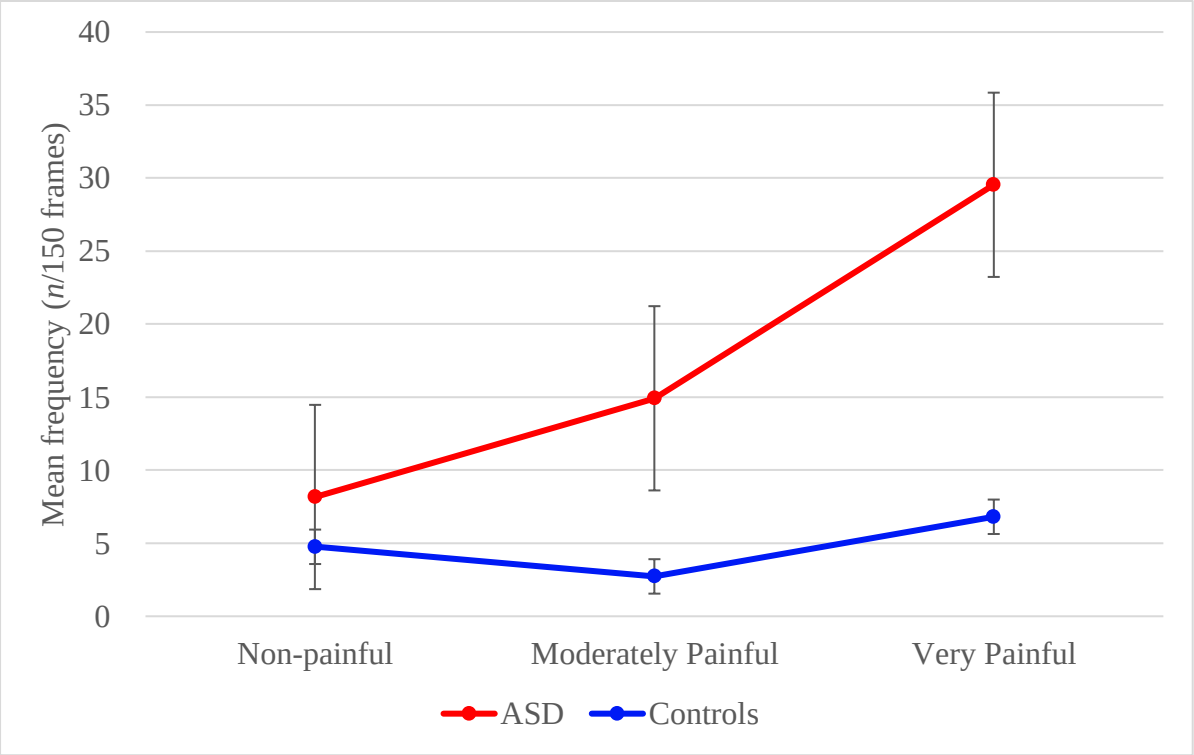


Note. Raw values given as mean and standard errors (*SE*) frames for thermal stimuli for each group. All significant $p < .05$.

For Lower Oblique, a 2 (Group [ASD/Controls]) *3 (Stimuli strength [non-painful/moderately painful/very painful]) mixed ANOVA revealed a significant between subjects factor main effect $F(1,14) = 5.816$, $p = .030$, $\eta_p^2 = .293$. It also revealed a significant main effect of stimuli strength and a main group*stimuli strength interaction $F(2,28) = 8.009$, $p = .006$, $\eta_p^2 = .364$, $F(2,28) = 4.881$, $p = .028$, $\eta_p^2 = .259$, respectively. Contrasts revealed that the frequency at which Lower Oblique units occurred increased as the temperature increased from non-painful to very painful ($F(1,14) = 8.820$, $p = .010$, $\eta_p^2 = .387$), and from moderately painful to very painful ($F(1,14) = 11.068$, $p = .005$, $\eta_p^2 = .442$). The interaction indicated that the frequency of Lower Oblique units for the different stimuli strengths differed between groups. In particular, the interaction graph (see figure 22) shows that although the frequency of Lower Oblique units increased as the temperature increased, this increase was most pronounced between the non-painful to very painful stimuli ($F(1,14) = 5.996$, $p = .028$, $\eta_p^2 = .300$) but not for moderately painful to very painful ($F(1,14) = 3.512$, $p = .082$, $\eta_p^2 = .201$). In particular, the ASD group showed a significant increase in frequency from non-painful to very painful ($t(7) = -2.957$, $p = .021$, $\delta = 1.190$). The ASD group also showed a significant increase in intensity from moderately painful to very painful ($t(7) = -2.826$, $p = .026$, $\delta = .752$). The control group showed no significant differences in intensity for any pairings ($t(7) = -.650$, $p = .536$, $\delta = .231$, $t(7) = -1.855$, $p = .106$, $\delta = .555$, $t(7) = .614$, $p = .559$, $\delta = .290$).

Figure 22.

Interaction graph for the frequency (n/150 frames) that Lower Oblique cluster occurred in Non-painful (41°C), Moderately painful (44°C) and Very-painful (47°C) heat stimuli for ASD and Control groups



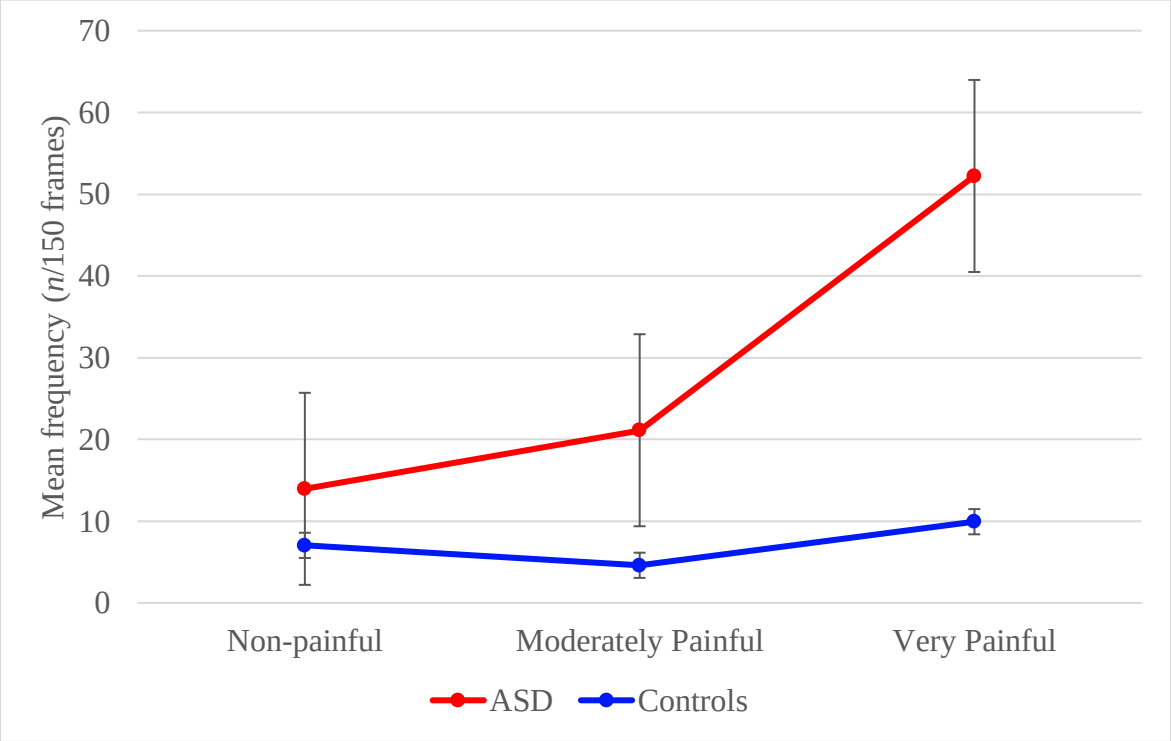
Note. Shows the interaction for group*stimuli strength for Frequency. Frequency is given as mean and standard error (*SE*).

To further explore which units within the Lower Oblique cluster were responsible for these effects, several 2 (Group [ASD/Controls]) *3 (Stimuli strength [non-painful/moderately painful/very painful]) mixed ANOVAs were conducted (AU11, AU12 and AU13, Nasolabial Furrow Deepener, Lip Corner Puller and Sharp Lip Puller, respectively). It revealed that the differences above were driven by both AU11 and AU12. Nasolabial Furrow Deepener (AU11) showed a main effect for group differences ($F(1,14) = 5.925$, $p = .029$, $\eta_p^2 = .297$), indicating that the ASD group displayed this more often than the controls. As well as that it occurred more frequently as temperatures increased ($F(2,28) = 8.272$, $p = .005$, $\eta_p^2 = .371$), as well as a significant group*stimuli intensity interaction ($F(2,28) = 5.455$, $p = .020$, $\eta_p^2 = .280$). Contrasts revealed that the frequency at which AU11 occurred increased as the temperature increased from non-painful to very painful ($F(1,14) = 8.529$, $p = .011$, $\eta_p^2 =$

.379), and from moderately painful to very painful ($F(1,14) = 14.019$, $p = .002$, $\eta_p^2 = .500$). The interaction indicated that the frequency of AU11 for the different stimuli strengths differed between groups. In particular, the interaction graph shows (see figure 23) that the frequency of AU11 increased as the temperature increased from non-painful to very painful stimuli ($F(1,14) = 6.298$, $p = .025$, $\eta_p^2 = .310$) as well as for moderately painful to very painful ($F(1,14) = 7.012$, $p = .019$, $\eta_p^2 = .334$). In particular, the ASD group showed a significant increase in frequency from non-painful to very painful ($t(7) = -2.894$, $p = .023$, $\delta = 1.161$). The ASD group also showed a significant increase in intensity from moderately painful to very painful ($t(7) = -3.440$, $p = .011$, $\delta = .939$). The control group showed no significant differences in intensity for any pairings ($t(7) = -.593$, $p = .572$, $\delta = .225$., $t(7) = -1.482$, $p = .182$, $\delta = .503$, $t(7) = .498$, $p = .634$, $\delta = .236$), therefore as stimuli increases in intensity to become painful the lines around the mouth and nose become deeper.

Figure 23.

Interaction graph for the frequency (n/150 frames) that the Action Unit Nasolabial Furrow Deepener (AU11) occurred in Non-painful (41°C), Moderately painful (44°C) and Very-painful (47°C) heat stimuli for ASD and Control groups

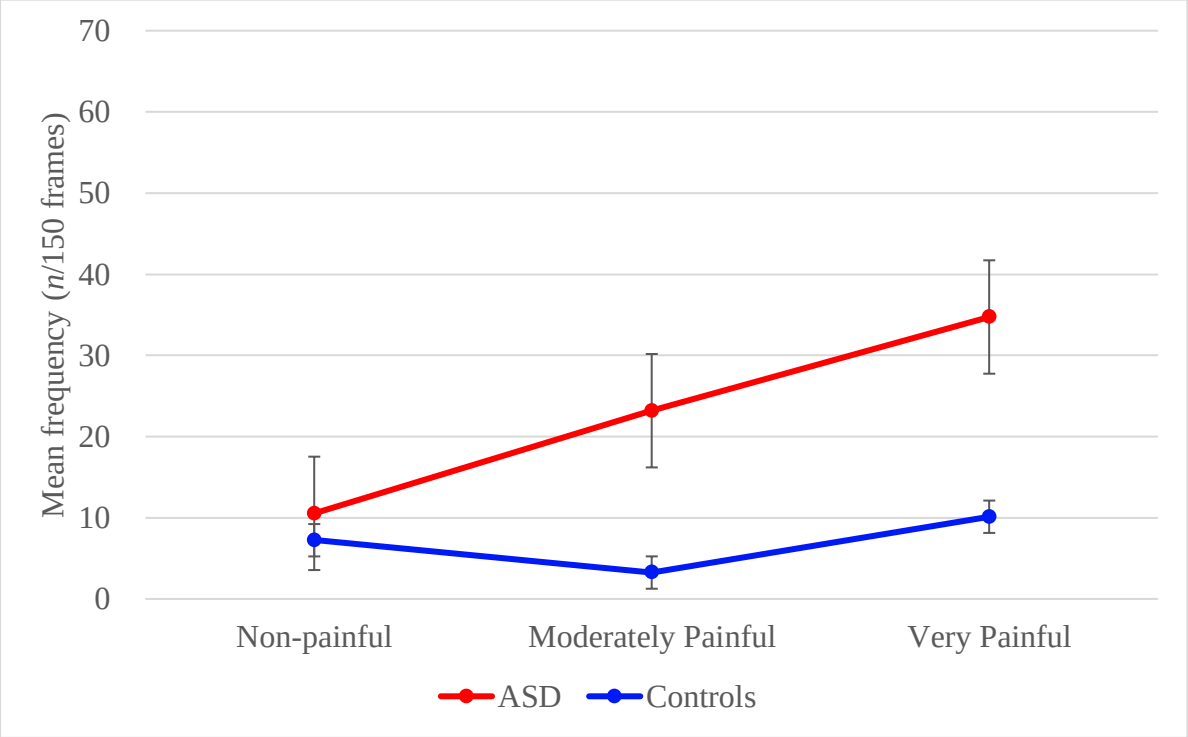


Note. Shows the interaction for group*stimuli strength for Frequency. Frequency is given as mean and standard error (*SE*).

Lip Corner Puller (AU12) showed a main effect for group differences ($F(1,14) = 4.777$, $p = .046$, $\eta_p^2 = .254$) and that it occurred more frequently as temperatures increased ($F(2,28) = 4.041$, $p = .029$, $\eta_p^2 = .224$). Although there was no significant interaction ($F(2,28) = 2.646$, $p = .089$, $\eta_p^2 = .159$), demonstrating that although Lip Corner Puller happened more frequently as the temperature arose, and that there were group differences, the intensity was not reliant on the group (see figure 24). Contrasts revealed that the frequency at which AU12 occurred increased as the temperature increased from non-painful to very painful ($F(1,14) = 4.858$, $p = .045$, $\eta_p^2 = .258$), and from moderately painful to very painful ($F(1,14) = 4.965$, $p = .043$, $\eta_p^2 = .262$).

Figure 24.

Interaction graph for the frequency (n/150 frames) that the Action Unit Lip Corner Puller (AU12) occurred in Non-painful (41°C), Moderately painful (44°C) and Very-painful (47°C) heat stimuli for ASD and Control groups



Note. Shows the interaction for group*stimuli strength for Frequency. Frequency is given as mean and standard error (*SE*).

For all other clusters 2 (Group [ASD/Controls]) *3 (Stimuli strength [non-painful/moderately painful/very painful]) mixed ANOVAs revealed no significant main effects of stimuli intensity or group*stimuli intensity interactions for frequency (p >.05; see table 21). Nor was there a main group effect (p >.05).

Table 22:

Descriptive statistics for all clusters for thermal stimuli strengths for ASD and Control groups

		Non-painful (41◦C)	Moderately painful (44◦)	Very painful (47◦C)
Cluster	**Group**			
Lower Vertical	ASD	9.93 (7.96)	9.74 (7.02)	15.42 (11.77)
	Controls	6.52 (7.77)	3.19 (4.57)	4.96 (6.01)
Lower Horizontal	ASD	1.99 (3.82)	2.61 (7.40)	7.03 (15.00)
	Controls	.33 (.94)	1.39 (5.22)	-
Misc.	ASD	.36 (1.02)	.63 (1.26)	.34 (.86)
	Controls	.17 (.49)	-	.07 (.20)
Eyes	ASD	8.26 (9.05)	6.39 (6.09)	6.03 (7.34)
	Controls	2.01 (4.26)	1.89 (5.17)	2.32 (5.75)
Gross Behaviour	ASD	3.75 (8.75)	3.13 (5.79)	5.59 (7.30)
	Controls	2.08 (5.88)	.52 (1.47)	.52 (1.47)

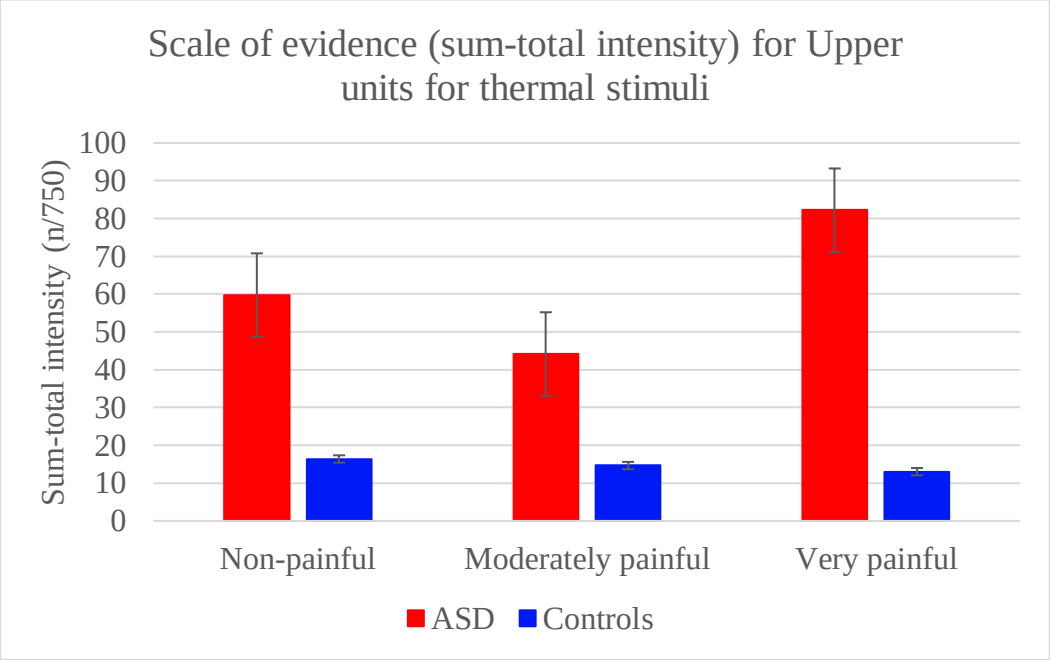
Note: All values given as mean (*SD*) frequency i.e., mean number of images (*n*/150) present in the clusters.

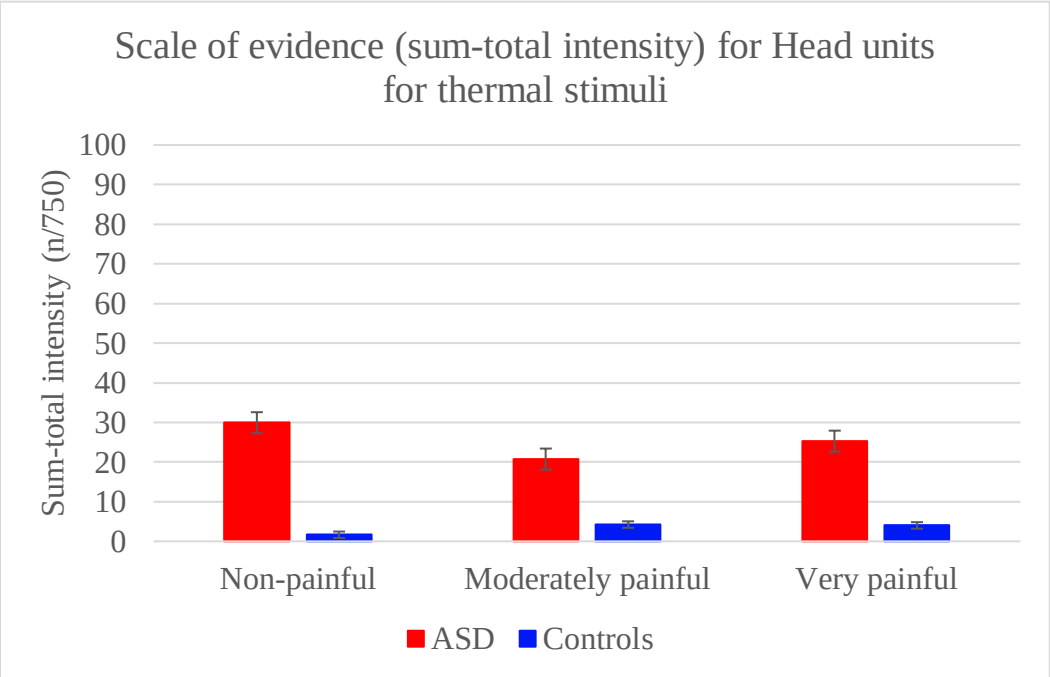
4.3.3.3 Sum-Total data for thermal stimuli (heat)

A series of 2 (Group [ASD/Controls]) *3 (Stimulus strength [non-painful/moderately painful/very painful]) mixed ANOVAs were run to determine group differences in clusters at different stimuli intensities for sum-total. Sum-total was the maximal intensity score for the cluster (sum total cluster = no. of units in group (150*5)). They revealed a significant main effect of group, for Upper ($F(1,14) = 11.955$, $p = .004$, $\eta_p^2 = .461$) and Head ($F(1,14) = 9.730$, $p = .008$, $\eta_p^2 = .410$) clusters, wherein the ASD group had greater frequency of facial expressions at every level of thermal stimuli, (see figure 25).

Figure 25.

*Maximal intensity score (sum-total = n/750 i.e., number of frames * 5) for clusters during Non-painful (41°C), Moderately painful (44°C), and Very-Painful heat stimuli (47°C) for ASD and Control groups*



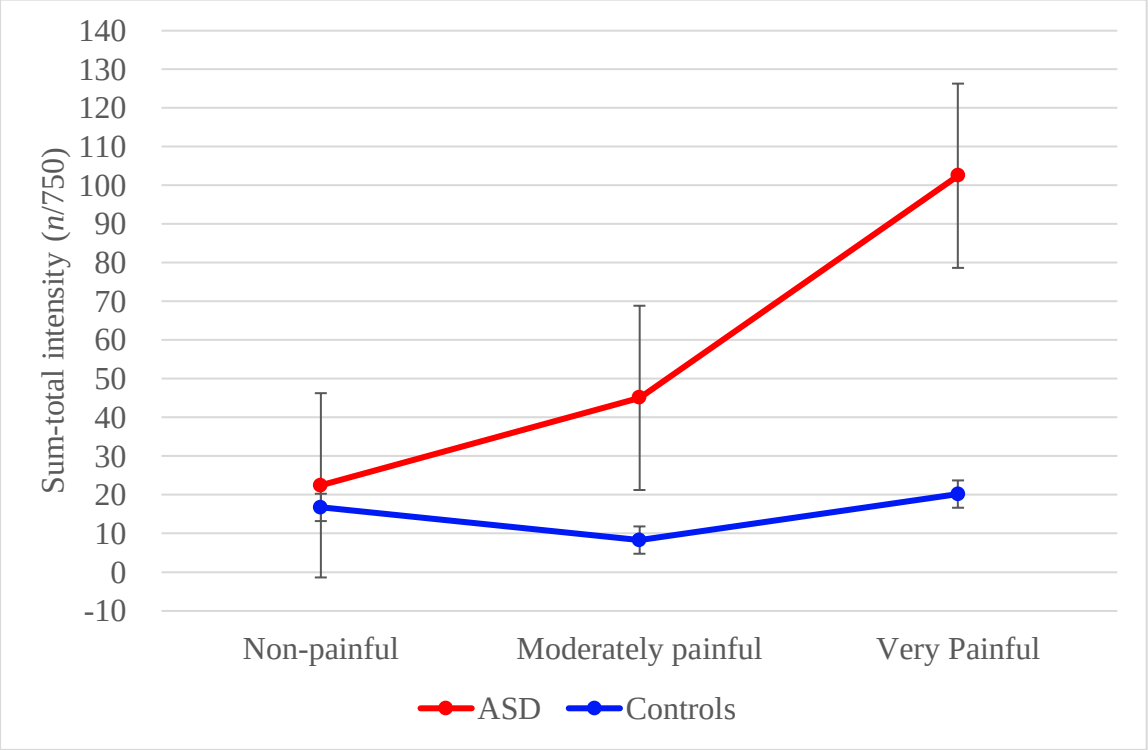


Note. Raw values given as mean and standard error (*SE*) sum-total score (n/750) for thermal stimuli for each group. All significant $p < .05$.

For Lower Oblique, a 2 (Group [ASD/Controls]) *3 (Stimuli strength [non-painful/moderately painful/very painful]) mixed ANOVA revealed a significant between subjects factor main effect $F(1,14) = 4.842$, $p = .045$, $\eta_p^2 = .257$. It also revealed a significant main effect of stimuli strength $F(2,28) = 6.990$, $p = .011$, $\eta_p^2 = .333$ and a significant group*stimuli strength interaction $F(2,28) = 5.196$, $p = .027$, $\eta_p^2 = .271$. Therefore, groups differed in their intensity for Lower Oblique units, and this intensity differed across the three stimuli. Contrasts revealed that the intensity of Lower Oblique units increased as the temperature increased from non-painful to moderately painful ($F(1,14) = 7.326$, $p = .017$, $\eta_p^2 = .344$), and very painful ($F(1,14) = 9.040$, $p = .009$, $\eta_p^2 = .392$). They also revealed the intensity increase of Lower Oblique units was most pronounced between the groups for the non-painful to very painful stimuli ($F(1,14) = 6.164$, $p = .026$, $\eta_p^2 = .306$, see figure 26) and in particular for the ASD group ($t(7) = -2.747$, $p = .029$, $\delta = 1.159$). The ASD group also showed a significant increase in intensity from moderately painful to very painful ($t(7) = -2.594$, $p = .036$, $\delta = .784$). The control group showed no significant differences in intensity for any pairings ($t(7) = .740$, $p = .483$, $\delta = .332$, $t(7) = -.340$, $p = .744$, $\delta = .111$, $t(7) = -1.848$, $p = .107$, $\delta = .521$).

Figure 26.

*Interaction graph for the maximal intensity score (sum-total = n/750 i.e., number of frames * 5) for Lower Oblique clusters during Non-painful (41°C), Moderately painful (44°C), and Very-Painful heat stimuli (47°C) for ASD and Control group*



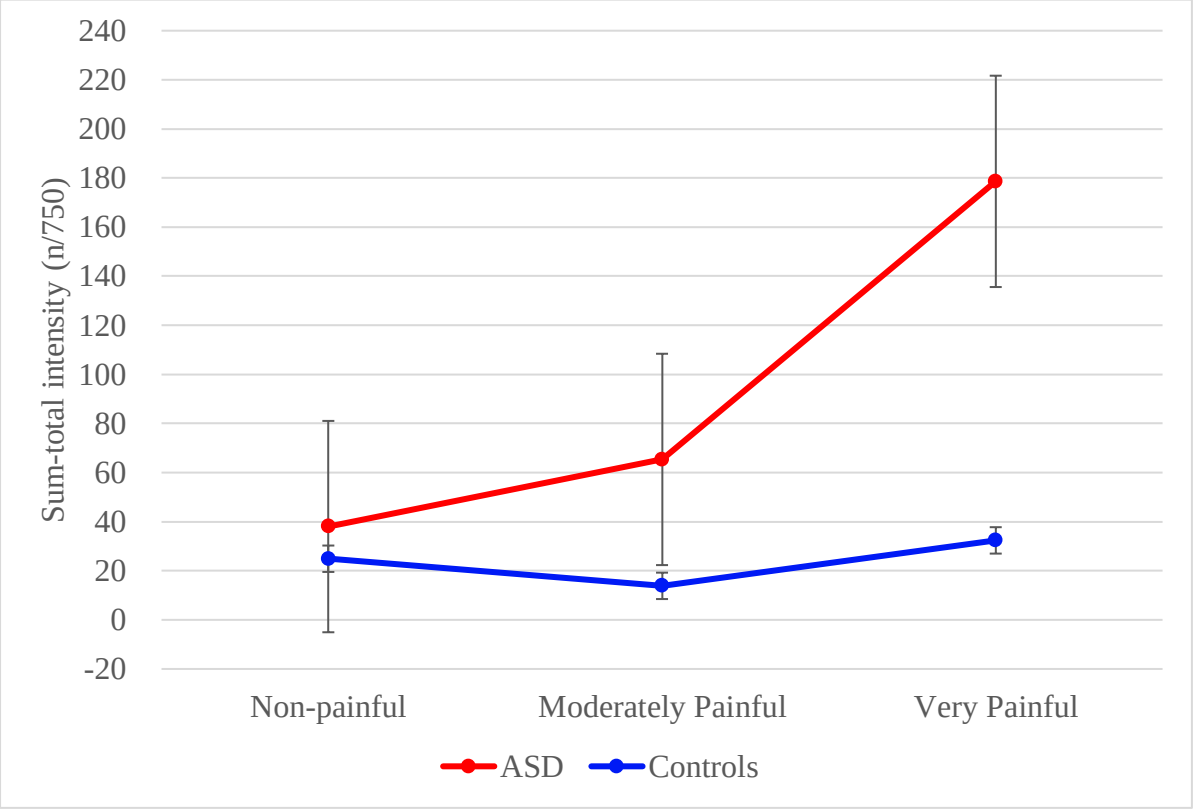
Note. Shows the interaction for group*stimuli strength for Frequency. Frequency is given as mean and standard error (*SE*) sum-total score (*n*/750).

To investigate this further, several 2 (Group [ASD/Controls]) *3 (Stimuli strength [non-painful/moderately painful/very painful]) mixed ANOVAs were conducted for each of the action units involved in the Lower Oblique cluster (AU11, AU12 and AU13, Nasolabial Furrow Deepener, Lip Corner Puller and Sharp Lip Puller, respectively). It revealed that the differences above were driven by AU11. Nasolabial Furrow Deepener (AU11) showed a main effect for group differences ($F(1,14) = 4.653$, $p = .049$, $\eta_p^2 = .249$) as well as an increase in intensity as temperatures increased ($F(2,28) = 8.313$, $p = .005$, $\eta_p^2 = .373$), as well as a significant group*stimuli intensity interaction ($F(2,28) = 5.920$, $p = .016$, $\eta_p^2 = .297$). Contrasts revealed that the intensity at which AU11 occurred increased as the temperature increased from non-painful to very painful ($F(1,14) = 8.583$, $p = .011$, $\eta_p^2 = .380$), and from moderately painful to very painful ($F(1,14) = 12.204$, $p = .004$, $\eta_p^2 = .466$). The interaction

indicated that the intensity of AU11 for the different stimuli strengths differed between groups. In particular, the interaction graph (see figure 27) shows that the intensity of AU11 increased as the temperature increased from non-painful to very painful stimuli ($F(1,14) = 6.937$, $p = .020$, $\eta_p^2 = .331$) as well as for moderately painful to very painful ($F(1,14) = 6.308$, $p = .025$, $\eta_p^2 = .311$). In particular, the ASD group showed a significant increase in intensity from non-painful to very painful ($t(7) = -2.906$, $p = .023$, $\delta = 1.166$). The ASD group also showed a significant increase in intensity from moderately painful to very painful ($t(7) = 3.160$, $p = .016$, $\delta = .917$). The control group showed no significant differences in intensity for any pairings ($t(7) = -.512$, $p = .624$, $\delta = .158$, $t(7) = -1.573$, $p = .160$, $\delta = .521$, $t(7) = .651$, $p = .536$, $\delta = .293$).

Figure 27.

*Interaction graph for the maximal intensity score (sum-total = n/750 i.e., number of frames * 5) that the Action Unit Nasolabial Furrow Deepener (AU11) occurred in Non-painful (41°C), Moderately painful (44°C) and Very-painful (47°C) heat s*



Note. Shows the interaction for group*stimuli strength for Frequency. Frequency is given as mean (*SE*) sum-total (n/750).

For all other clusters 2 (Group [ASD/Controls]) *3 (Stimuli strength [non-painful/moderately painful/very painful]) mixed ANOVAs revealed no significant main effects of stimuli intensity or group*stimuli intensity interactions for frequency (p >.05; see table 22). Nor was there a main group effect (p >.05).

Table 23:

Descriptive statistics for all clusters for thermal stimuli strengths for both ASD and Control groups

		Non-painful (41◦C)	Moderately painful (44◦C)	Very painful (47◦C)
Cluster	**Group**			
Lower Vertical	ASD	27.64 (20.89)	26.11 (21.77)	49.68 (45.18)
	Controls	20.83 (27.73)	8.58 (13.12)	13.54 (17.74)
Lower Horizontal	ASD	7.06 (14.87)	9.54 (26.99)	24.80 (55.33)
	Controls	1.40 (3.95)	.63 (1.77)	-
Lower Orbital	ASD	15.56 (9.76)	17.07 (12.07)	31.71 (32.13)
	Controls	.56 (1.58)	.80 (1.48)	5.04 (6.51)
Misc.	ASD	1.37 (3.63)	2.33 (4.58)	1.08 (2.66)
	Controls	.74 (2.09)	-	.19 (1.91)
Eyes	ASD	26.74 (33.54)	17.46 (17.70)	18.61 (22.09)
	Controls	6.11 (12.21)	5.36 (14.42)	7.04 (16.68)
Gross Behaviour	ASD	6.54 (16.03)	6.77 (11.77)	11.97 (15.95)
	Controls	3.64 (10.29)	1.04 (2.95)	.52 (1.47)

Note: All values given as mean (*SD*) Sum-total intensity (*n*/750) for the cluster. ASD (Autism Spectrum Disorder)

4.3.4 Facial Expressions of Pain to Cold Pressor Stimuli

4.3.4.1 Present/Absent data for Cold Pressor Stimuli

As the expected count assumption was not met, Fisher's exact test is reported for all clusters (see table 23). For cold pressor sensation, pain, and tolerance the ASD group did not significantly differ in their facial expressions compared to controls ($p>.05$), although, of note is that Lower Vertical expressions were present in the entire sample (see table 23).

Table 24:

Fishers exact tests for all clusters for Cold Pressor Stimuli for ASD and Control groups

Cluster	**ASD (n)**		**Controls (n)**		***p value***	***Odds ratio***
Cold Pressor Sensation	Present	Absent	Present	Absent		
Neutral (AU0)	5	3	5	3	.696	1.000
Upper	8	-	7	1	.500	1.143
Lower Vertical	7	1	4	4	.141	.143
Lower Horizontal	1	7	-	8	.500	.875
Lower Oblique	3	5	4	4	.500	.875
Lower Orbital	2	6	-	8	.233	.750
Misc.	-	8	1	7	.500	1.143
Head	5	3	6	2	.500	1.800
Eyes	3	5	3	5	.696	1.000
Cold Pressor Pain						
Neutral (AU0)	1	7	4	4	.141	7.000
Upper	8	-	6	2	.233	1.333
Lower Vertical	8	-	8	-	-	-
Lower Horizontal	2	6	0	8	.233	.750
Lower Oblique	7	1	4	4	.141	.143
Lower Orbital	5	3	3	5	.310	.360
Misc.	1	7	1	7	.767	1.000
Head	5	3	2	6	.157	.200
Eyes	4	4	3	5	.500	.600
Gross Behaviour	1	7	1	7	.767	1.000
Cold Pressor Tolerance						
Neutral (AU0)	1	7	3	5	.285	4.200
Upper	8	-	7	1	.500	1.143
Lower Vertical	5	3	3	5	.310	.360
Lower Horizontal	1	7	-	8	.500	.875
Lower Oblique	5	3	3	5	.310	.360
Lower Orbital	2	6	1	7	.500	.429
Misc.	1	7	-	8	.500	.875
Head	7	1	5	3	.285	.238
Eyes	4	4	5	3	.500	1.667
Gross Behaviour	1	7	1	7	.767	1.000

Note. All values given as *n* = number of participants. ASD (Autism Spectrum Disorder).

4.3.4.2 Frequency Data for Cold Pressor Stimuli

T-tests or Mann Whitney *U* tests (were KS test revealed assumptions of normality were violated) revealed that for cold pressor sensation, pain, and tolerance, at least in terms of the maximal presence of an action unit observed for the duration of the stimulus, the frequency of facial expressions did not significantly differ between the ASD group and controls (see table 24).

Table 25:

Descriptive and test statistics including effects sizes for all clusters for Cold Pressor Stimuli for ASD and Control groups

Clusters	ASD	Controls	*Test Value*	*p value*	*Effect Size*
Cold Pressor Sensation					
Neutral (AU0)+	53.63 (56.50)	49.63 (56.92)	30.500	.871	r = -.04
Upper	3.56 (3.06)	6.59 (5.89)	-1.292	.217	δ = .65
Lower Vertical	8.09 (6.80)	5.39 (6.93)	.788	.444	δ = .39
Lower Horizontal+	.44 (1.24)	-	28.000	.317	r = .25
Lower Oblique+	5.91 (9.69)	25.96 (43.79)	28.000	.643	r = -.12
Lower Orbital+	1.40 (3.57)	-	24.000	.144	r = -.37
Misc.+	-	.03 (.10)	28.000	.317	r = -.25
Head+	.63 (.52)	.75 (.46)	28.000	.602	r = -.13
Eyes+	5.72 (10.38)	2.97 (5.58)	30.500	.856	r = -.05
Cold Pressor Pain					
Neutral (AU0)+	8.13 (22.98)	32.75 (58.85)	20.000	.125	r = -.38
Upper	17.38 (13.00)	7.89 (7.97)	1.759	.100	δ = .88
Lower Vertical+	13.39 (10.57)	10.34 (12.98)	24.000	.394	r = -.26
Lower Horizontal+	5.69 (12.84)	-	24.000	.144	r = -.37
Lower Oblique	34.54 (35.37)	25.75 (36.05)	.348	.733	δ = .23
Lower Orbital+	4.00 (4.33)	1.15 (1.88)	19.500	.161	r = -.35
Misc.+	1.30 (3.66)	.30 (.84)	31.500	.927	r = -.02
Head+	10.71 (9.15)	2.49 (5.34)	16.500	.070	r = -.45
Eyes+	4.88 (7.53)	4.77 (7.81)	30.000	.817	r = -.06
Gross Behaviour+	3.13 (7.81)	3.13 (8.84)	32.000	1.000	-
Cold Pressor Tolerance					
Neutral (AU0)+	6.50 (18.38)	37.50 (66.77)	23.500	.241	r = -.29
Upper	19.67 (15.20)	14.92 (15.85)	.612	.550	δ = .30
Lower Vertical+	10.11 (10.76)	7.75 (12.02)	25.500	.466	r = -.18
Lower Horizontal+	7.25 (20.51)	-	28.000	.317	r = -.25
Lower Oblique+	30.00 (40.18)	24.79 (38.08)	27.500	.614	r = -.13
Lower Orbital+	2.35 (5.95)	.23 (.64)	27.500	.487	r = -.17
Misc.+	.07 (.19)	-	28.000	.317	r = -.25
Head	15.76 (11.89)	7.21 (8.02)	1.686	.114	δ = .84
Eyes+	5.42 (7.49)	3.95 (4.73)	31.000	.913	r = -.03
Gross Behaviour+	3.00 (8.49)	3.13 (8.84)	31.500	.927	r = -.02

Note. All values given as mean (*SD*) frequency i.e., mean number of images (n/150) the clusters were present in. + indicates those clusters who did not meet parametric assumptions and Mann Whitney *U* was conducted. All values are given as mean (*SD*) rather than rank to facilitate understanding and comparisons. Effect sizes given as Cohen's δ for parametric t-tests, or *r* for non-parametric Mann Whitney *U*.

4.3.4.3 Sum-total Data for Cold Pressor Stimuli

T-tests or Mann Whitney *U* tests (where assumptions were violated) revealed that for cold pressor sensation, pain, and tolerance, there were no significant group differences between the sum-total intensity of facial expressions (see table 25). Suggesting that, facial

expression, at least in terms of the maximal intensity of an action unit observed for the duration of the stimulus, are similar between the ASD group and controls.

Table 26:

Descriptive and test statistics including effects sizes for all clusters for Cold Pressor Stimuli for ASD and Control groups

Cluster	ASD	Controls	*Test Value*	*p value*	*Effect Size*
Cold Pressor Sensation					
Upper	3.56 (3.06)	6.59 (5.89)	-1.530	.161	δ = .65
Lower Vertical+	18.52 (14.73)	16.12 (18.88)	28.000	.670	*r* = -.11
Lower Horizontal+	.88 (2.47)	-	28.000	.317	*r* = -.25
Lower Oblique+	19.63 (26.46)	85.92 (160.82)	28.000	.643	*r* = -.12
Lower Orbital+	3.53 (9.26)	-	24.000	.144	*r* = -.37
Misc.+	-	.14 (.39)	28.000	.317	*r* = -.25
Head	22.63 (24.73)	10.20 (14.93)	1.217	.248	δ = .61
Eyes+	15.14 (29.58)	8.69 (16.06)	31.500	.952	*r* = -.02
Cold Pressor Pain					
Upper	62.03 (56.15)	26.00 (25.22)	1.656	.120	δ = .83
Lower Vertical	39.47 (37.81)	27.78 (32.31)	.665	.517	δ = .33
Lower Horizontal+	20.56 (49.70)	-	24.000	.144	*r* = -.37
Lower Oblique+	113.79 (123.70)	91.21 (135.76)	23.000	.337	*r* = -.24
Lower Orbital+	13.60 (16.30)	4.20 (7.46)	20.500	.197	*r* = -.32
Misc.+	6.48 (18.32)	1.05 (2.96)	31.500	.927	*r* = -.02
Head+	24.79 (22.89)	6.74 (15.77)	18.000	.104	*r* = -.41
Eyes+	12.66 (18.09)	15.19 (24.09)	32.000	1.000	-
Gross Behaviour+	15.63 (44.19)	6.25 (17.68)	31.500	.927	*r* = -.02
Cold Pressor Tolerance					
Upper	68.47 (56.67)	46.58 (49.58)	.822	.425	δ = .41
Lower Vertical+	29.47 (31.92)	22.64 (32.97)	25.500	.537	*r* = -.15
Lower Horizontal+	27.75 (61.52)	-	28.000	.317	*r* = -.25
Lower Oblique+	118.67 (182.89)	79.54 (127.23)	25.500	.466	*r* = -.18
Lower Orbital+	11.30 (29.84)	.55 (1.56)	27.000	.441	*r* = -.19
Misc.+	.20 (.58)	-	28.000	.317	*r* = -.25
Head	44.09 (31.07)	20.15 (21.99)	1.79	.097	δ = .89
Eyes+	13.91 (18.32)	13.78 (16.02)	31.000	.913	*r* = -.03
Gross Behaviour+	9.00 (25.46)	12.50 (35.36)	31.500	.927	*r* = -.02

Note. All values given as mean (*SD*) sum-total (i.e., maximal intensity) of the clusters. + indicates those clusters who did not meet parametric assumptions and Mann Whitney *U* was conducted. All values are given as mean (*SD*) rather than rank to facilitate understanding and comparisons. Effect sizes given as Cohen's δ for parametric t-tests, or *r* for non-parametric Mann Whitney *U*.

4.3.5 Self-report Ratings of Thermal Stimuli

Participants were asked if each of the thermal stimuli were painful or not. Fishers exact test revealed no significant group differences for non-painful (p =.233, OR = 2.333) or moderately painful thermal stimuli (p = .500, OR = 1.800). *T*-tests used to determine if the

ASD group differed in their self-reported ratings of pain intensity and unpleasantness for non-painful, moderately painful, and very painful thermal stimuli compared to controls revealed no significant group differences (see table 26). Despite there being no significant group differences, the ASD group reported greater intensity and unpleasantness for each stimulus compared to controls, indicating a greater sensitivity for aversive experience.

Table 27:

Descriptive statistics and test values including effect sizes for self-reported pain intensity and unpleasantness of Non-painful (41◦C), Moderately painful (44◦C) and Very-painful (47◦C) heat stimuli for ASD and Control groups

		ASD	**Controls**	***Test value***	***p value***	***Effect size***
Intensity	Non-painful	2.19 (2.03)	1.31 (1.03)	1.085	.303	.547
	Moderately painful	4.19 (1.98)	3.19 (2.12)	.975	.346	.488
	Very painful	6.75 (1.67)	5.69 (1.49)	1.345	.200	.670
Unpleasantness	Non-painful	1.69 (1.81)	1.06 (1.05)	.844	.413	.426
	Moderately painful	4.31 (2.14)	2.31 (1.71)	2.067	.058	1.033
	Very painful	6.81 (1.10)	5.81 (1.53)	1.499	.156	.750

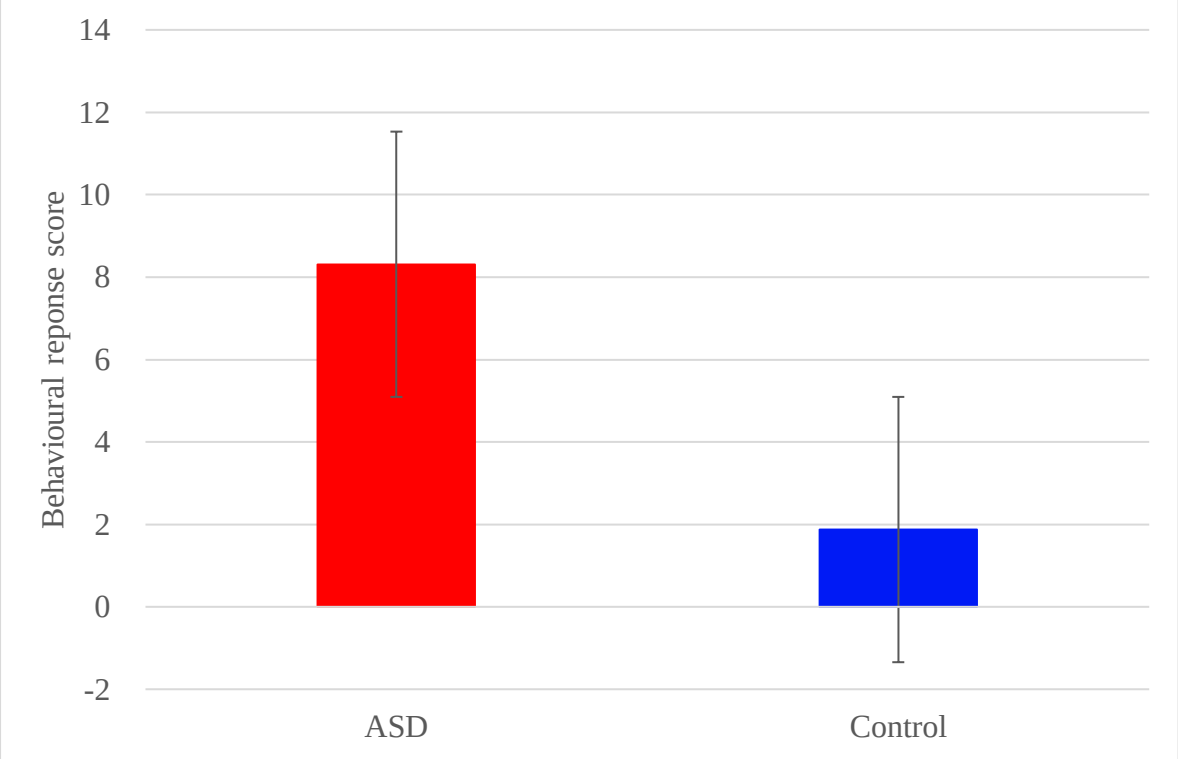
Note. Values given as mean (*SD*).

4.3.6 Behavioural Responses

T-test revealed that there was a significantly greater behavioural response to stimuli in the ASD group compared to controls $t(14) = 3.188$, $p = .013$, $\delta = 1.661$ (see figure 28). This supports the findings from the facial expression data in that the ASD group were generally more expressive facially. Findings indicate that the ASD group were generally more expressive, and this was true for global behaviours measured by the NCAPC. Pain expression outside of the face was greater in the ASD group compared to controls. Controls had less pain expression both facially and outside of the face.

Figure 28.

Behavioural response mean score as derived from the Non-Communicating Adults Pain Checklist (n/51) for ASD and Control groups for the duration of the experiment



Note. Values given as mean (*SE*).

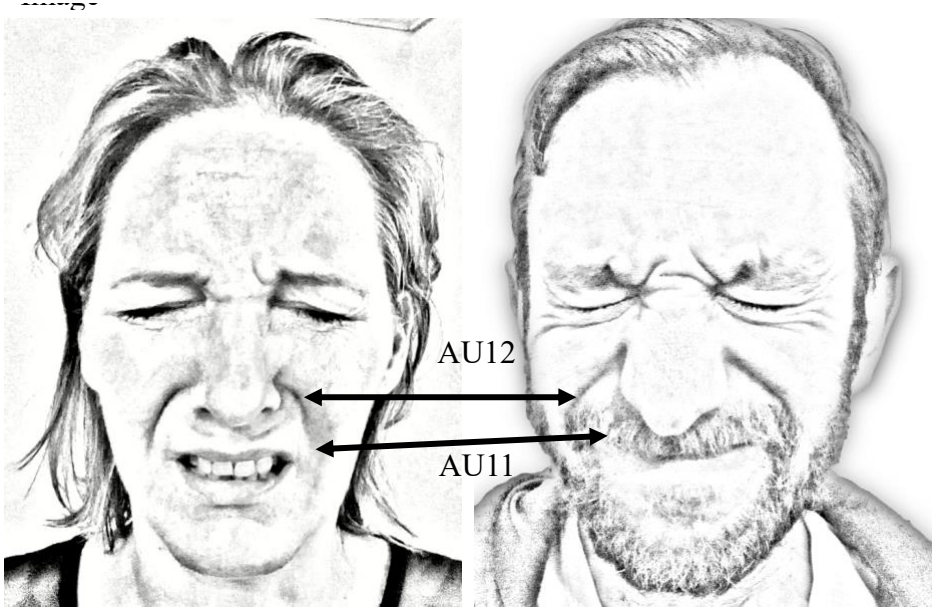
4.3.7 Summary of findings

To summarise the complex findings from this Chapter presented below is a figurative representation and a table of the significant effects reported above. Altogether, facial expression of pain for cold and hot thermal stimuli appears to be similar for both the ASD group and controls (see figure 29, Image A), results however, point to some important nuances in the expression (See figure 29, Image B). Lower Oblique seems particularly expressive of pain in ASD both in terms of its frequency and intensity (see figure 29 and table 27).

Figure 29.

Examples of Action Units and facial expressions reported as significantly different between ASD and Control group

Controls more likely to show a Neutral expression unless stimulus was very painful (AU0).



Facial expression, for cold and hot thermal stimuli is similar for controls (left image B) and ASD (right image B). Lower Oblique, particularly Nasolabial Furrow Deepener (AU11) and Lip Corner Puller (AU12), seem particularly expressive of pain in ASD, both for frequency and intensity for hot thermal painful stimuli.

All images in the above figure, belong to the author of this thesis, having been photographed, edited, and adapted by the author (SV) for the purposes of generating this diagram.

Table 28:

Summary of the main significant findings from this experiment

Cluster	**Unit Number**	**Unit Description**	**Present/Absent**			**Frequency**			**Sum-Total**		
			Chi Squared Between Group			**Main Effects**		**Interaction**	**Main Effects**		**Interaction**
			Non Painful	*Moderately Painful*	*Very Painful*	*Between Groups*	*Stimulus Type*		*Between Groups*	*Stimulus Type*	
Neutral	AU0	Neutral	✓	✓		✓			-	-	-
Upper						✓			✓		
Lower						✓	✓	✓	✓	✓	✓
Oblique	AU11	Nasolabial Furrow				✓	✓	✓	✓	✓	✓
	AU12	Deepener				✓	✓				
	AU13	Lip Corner Puller									
		Sharp Lip Puller									
Lower Orbital			✓			✓					
Head						✓			✓		
Eyes				✓							

Note. ✓ signifies significant differences (p<.05).

4.4 Discussion

The current experiment investigated the communications of pain in ASD, specifically participants facial and behavioural expressions were video recorded during application of different intensities of heat stimuli that were applied in a random order, and during a cold pressor task. Videos were then coded using the FACS and the NCAPC. Altogether, facial expression of pain for cold and hot thermal stimuli appears to be similar for both autistic individuals and controls. Results however, point to some important nuances in the expression. For the ASD group, Upper, Lower Orbital and Head Movements occurred at greater frequency during any thermal stimuli for ASD. Upper and Head Movements in particular also occurred at a greater intensity. Lower Oblique seems particularly expressive of pain in ASD both in terms of its frequency and intensity. This was driven by Nasolabial Furrow Deepener and Lip Corner Puller where they occurred more frequently in ASD than controls. For Nasolabial Furrow Deepener, not only was there greater activity, but it also presented more intensely, and intensity increased as stimulus intensity increased. Additionally, controls were more likely to show neutral expressions compared to the ASD group unless the stimulus was very painful. These findings stand in contrast to anecdotal evidence that suggests an insensitivity or indifference to pain in autistic individuals.

This experiment is the first of its kind to investigate facial expressions to both tonic and phasic hot and cold noxious stimuli in autistic adults using the full FACS system and the NCAPC. With regards to facial responses assessed, units found to represent pain in ASD, namely the Lower Oblique units described above are not in line with previous findings on facial expressions of pain. Facial units associated with painful stimuli are typically those housed under the Lower Vertical or Horizontal cluster (Craig et al., 1991; LeResche, 1982; LeResche & Dworkin, 1988; Patrick et al., 1986; Prkachin, 2009) not the Lower Oblique

cluster. In particular, the Nasolabial Furrow Deepener, not only occurred more frequently, like other units in this cluster, but it also increased in intensity as the intensity of the painful stimuli increased. This stands together with ASD findings that shows a differing response to pain (Nader et al., 2004; Rattaz et al., 2013; Tordjman et al., 2009), one that may not be expected by observers who would be seeking the more commonly associated lower vertical or horizontal movements – such as upper lip raiser. However, there is not enough substantial evidence specifically in this area to generate a theory as to why Lower Oblique facial expressions might be particularly indicative of pain in ASD. Drawing on the evidence in relation to social contagion, mimicry, and eye gaze patterns in relation to autism provides both potential avenues for further investigations and explanations. Research has shown that autistic individuals look less at the eye region of expressive faces (Corden et al., 2008; Pelphrey et al., 2002) or do not use information from upper aspects of the face as effectively during identification of emotions (Baron-Cohen et al., 1997; Gross, 2008; Spezio et al., 2007a, 2007b). Whilst there is evidence to suggest greater reliance on information from the lower aspects of the face (Gross, 2004; Neumann et al., 2006; Spezio et al., 2007a, 2007b), other researchers argue that this is not because they are more perceptually interesting than the eyes but that there is a top-down modulation or dysfunction (Neumann et al., 2006; Pelphrey et al., 2002). Furthermore, autistic individuals display a reduced mimicry of others' facial expressions (Beall et al., 2008; McIntosh et al., 2006; Wieckowski & White, 2017; Yoshimura et al., 2015) or less accurate (Harms et al., 2010) or delayed mimicry (Oberman et al., 2009). Specifically, there is some evidence of greater mimicry occurring for the zygomaticus (Beall et al., 2008) than muscles in the upper regions of the face from the electromyography (EMG) research. Delayed mimicry and a poorer ability to recognise surprise was also reported in autistic individuals – an emotion most expressed through the upper regions of the face (Wieckowski & White, 2017). Supporting data from the FACS

analysis conducted by (Yoshimura et al., 2015), showed that mimicry was poorer for brows being lowered (AU4 Brow Lowerer) than an expression in the lower region of the face, namely, Lip Corner Puller (AU12). Interestingly this latter action unit is housed under the Lower Oblique cluster and so our findings are directly comparable here. Therefore, it is possible that autistic individuals have learned expressions through a social contagion of the lower regions of the face which may then account for lower oblique movements being a greater indicator of pain in ASD.

A further potential explanation of the increased facial reactivity observed in this experiment, is related to social context. Display rules, driven by the social context, dictate how and if expressions are modulated (Robbins & Vandree, 2009; Smoski & Bachorowski, 2003) especially painful expressions whose aim is to invoke help from others (Craig, 2015). Since ASD is characterised by social impairment (APA, 2013) it is not surprising that the details of the social environment or perceptions of perceived sociability or lack thereof, may influence the expressions of pain. Research has shown that autistic individuals are less spontaneously expressive than controls in social environments (Kasari et al., 1990; Yirmiya et al., 1989). As well as displaying more intense, frequent, and spontaneous facial expressions in a non-social environment than during an interaction with another person (Faso et al., 2015; Zane et al., 2018). Research has also highlighted that facial expressions autistic individuals are less likely to be initiated for social communication purposes, and seemed incongruous to the social context in which they were expressed (Trevisan et al., 2018). It is possible, that once the researcher was out of sight, autistic individuals were unable to gauge the attention of the researcher which encouraged them to be uninhibited in their response (Trevisan et al., 2018), therefore resulting in greater expressive communication than is typically observed in the anecdotal evidence. This contrasts with controls who follow the display rules dictated by the social context. When typically developing children are observed

they show more facial expression in the presence of a parent, or during the recovery periods where help seeking is likely to be initiated (Vervoort et al., 2011; Vlaeyen et al., 2009). Pain expression in typically developing individuals is also dependent on the relationship with the individual observing them, for example some research has shown that the mere presence of a researcher can inhibit pain response supporting this notion (Krahé et al., 2013). In our controls there appeared to be an inhibition of pain facial expressions, even though intensity scores were similar across both groups. It is likely that expressions were inhibited as the researcher could be perceived a stranger, or again they may have felt that they were unobserved and so display rules suggested there was no one with which to communicate their pain. Although it is difficult to know whether social context does play a role in pain expressions in ASD, as research instead has focussed on posed or naturally occurring expressions including smiles, laughter, and fear. Correlations between social communication, social reciprocity overall AQ scores and overall facial expressiveness may go some way to supporting this notion and is one area which future research should consider. Particularly once a greater consensus has been reached around which units are likely expressive of pain in ASD.

Our findings showed that individuals without ASD were also more likely to remain neutral in their expression, compared to autistic individuals. These findings stand in contrast to many of the autobiographical (Bemporad, 1979; Elwin et al., 2012) and clinical observation work (Gillberg & Coleman, 2000; Mahler, 1952) that reports insensitivity to pain, as well as the DSM-5 criteria (APA, 2013). Much of this work describes and focuses on the lack of withdrawal reflexes or unusual active behaviours, such as biting or holding a lighter to a lip until there is tissue damage. Even when quantitative measures are obtained, the emphasis is on active behaviours, with a remaining focus on withdrawal or pain avoidance behaviours or verbal reports (Muskat et al., 2014) with less if any focus on facial

4173 expression. Parents are asked broad encompassing questions without specification about
4174 what reactions to consider (Klintwall et al., 2011; Militerni et al., 2000; Olof Dahlgren &
4175 Gillberg, 1989). When facial expression is measured, such as here, findings converge on
4176 facial expression of pain being present in ASD, although these may be more nuanced (as in
4177 our study with lower oblique units) or more complex (Nader et al., 2004; Rattaz et al., 2013).
4178 A further potential explanation for this could be the result of an anticipatory distress of novel
4179 stimuli (Moore, 2015; Vivanti et al., 2018). For example, in the study by Nader et al., (2004),
4180 children with ASD were wrapped in a blanket prior to venepuncture, and controls were not.
4181 Results showed increased behavioural distress prior to needle insertion, supporting this notion
4182 of anticipatory distress. Additionally, findings from this experiment support those of Nader
4183 et al., (2004) as there were also group differences in behavioural responses as coded by the
4184 NCAPC. The NCAPC measures a range of behavioural non-verbal cues and this was applied
4185 to the entire duration of the experiment, rather than segments. The differences here, in terms
4186 of ASD compared to controls showing increased behavioural responses which does not match
4187 the facial activity data, could be the result of anticipatory distress being present from the
4188 beginning.

4189 Findings from this experiment should also be considered in light of several
4190 limitations. The first of which relates to a difference in psychophysical testing of cold
4191 pressor tolerance. In the current sample, the ASD group had a significantly lower tolerance
4192 for pain during a cold pressor task compared to controls which stands in contrast to the lack
4193 of differences reported in a previous Chapter (see Chapter 2 Vaughan et al., 2019). This
4194 highlights the difficulty in generalising findings to the wider autism phenotype. Instead
4195 adding to the argument of a heterogenous group which extends to the differences in
4196 psychophysical responses (Fründt et al., 2017; Vaughan et al., 2019). Furthermore, this
4197 highlights the increasing importance of considering individual differences in the phenotypic

presentation of pain in ASD. Secondly, as discussed in all previous Chapters, and consistent with other published research in the field, sample size continues to be small resulting in the risk of type II errors which limits the ability to generalize findings to the wider ASD population. As with small sample sizes, variance is a problem. However, with FACS data, there is an added risk of floor and ceiling effects in the data, in which case variance is not measured or estimated above a certain level (Garin, 2014; Salanti & Ioannidis, 2009). This can be a likely effect for FACS data, where maximal intensities are easier to identify (i.e., 5,4,3 representing maximum, severe, or marked pronounced). This is represented in FACS training where certification is focussed around an individual's ability to recognise expressions at these intensities, with acknowledgement that trace of slight movements' can be more difficult to observe, particularly in moving clips (Ekman, 1992). It is therefore likely that floor and ceiling effects are present in the data set. However, as our analysis was conducted on stills taken from the videos and with a higher frame rate this should allow for some variance to be captured and reduce the likelihood of these floor and ceiling effects. Observer reliability is a defence against observations that are superfluous, providing confirmatory analysis of the data and in ideal circumstances should be conducted. However, this was unable to be conducted within this experiment, both due to lack of access to a trained FACS coder and to changes in GDPR regulations that hindered use of FACS software at a partner institution. In this instance, the GDPR changes came after data had been collected and the limitation here was in being ethically able to re-seek consent from participants who had consented to particular usage of their data, which did not include future contact. In the previous Chapter, working across laboratories was given as a solution to solving sample size issues (Button et al., 2013; Christley, 2010), but this might be similarly a consideration when attempting to find a second coder. In light of GDPR changes, seeking consent from participants to share with the specified institution and/or person is a first step to consider, as

well as ensuring there is a legal contract in place with those institutions who sit outside the EU GDPR regulations. Working within the EU and its institutions is a simpler solution as data safety is consistent in these nation states.

Alongside the increase in sample size, and given the aforementioned theoretical underpinnings discussed future research should also consider the incorporation of EMG in their methodology. EMG recordings from the zygomaticus and the corrugator would help differentiate between potential observable expressions and micro expressions that an observer may be less able to detect (Beall et al., 2008; Bhushan, 2015; Wieckowski & White, 2017). This would not only solve issues related to observer bias, but it could also provide a measure of muscle activation to support the findings from FACS that again could be more objective. Results could then be correlated to determine the difference between micro and expressive emotion. This may go some way in explaining the observation of insensitivity to pain in ASD, if those upper facial units typically associated with an expression of pain are micro expressed in ASD and therefore less observable with the naked eye compared with the more visually expressive lower regions. Research should also consider the importance of social context. Adopting differing degrees of social interaction, such as the degree of observation (direct or indirect), will address the theory that it is how and when to express pain that impedes on the natural expression of pain in ASD (Faso et al., 2015; Trevisan et al., 2018; Zane et al., 2018).

To conclude, this experiment investigated pain expression towards experimental cold and hot thermal stimuli in ASD. Findings reveal that the insensitivity observed in anecdotal accounts is not due to an inability to produce facial expressions, but that there may be an ASD specific pain expression particularly focussed on the lower oblique movements. It may be likely that when in a lab where they are not directly observed by an individual, autistic

individuals are able to express pain in a more natural way. These findings are tentative, and the results are limited in terms of supporting or refuting those previously reported. However, this experiment does provide a strong methodological contribution to this area of research. This first-of-its-kind experiment has highlighted some interesting areas to consider for future development. For example, it may be important to consider the link between social deficits, social context and pain expression. Establishing this through replication and further investigation is an important step in further explaining the observational and anecdotal claims of altered behaviour, whilst also looking for alternative ways to work in order to improve sample sizes to increase power. Lastly, an important step would be to replicate this methodology whilst pairing with EMG to determine differences in muscle activity for lower and upper regions of the face, which may go some way at determining differences between micro expressions and those that may be more observable.

Chapter 5. General Discussion

Chapter 5.

5.1 Overview of the Findings

The aim of this thesis was to experimentally investigate pain in ASD compared to controls to determine whether under controlled conditions: 1) there was a difference in processing of pain stimuli applied based on psychophysical principals, 2) there was a greater attenuation of avoidance behaviours by a valued reward and 3) there was a difference in the facial communication of pain, to expand understanding of where in the pain process differences occurred that could account for the altered behaviours observed in the anecdotal evidence.

5.1.1 Peripheral processing of a stimulus evoked response

All experiments presented here used psychophysically robust techniques to systematically test pain thresholds. In experiments 3 (Chapter 3. Attenuation of Avoidance Behaviour Towards Pain by a Competing Goal) and 4 (Chapter 4: Expressions of Acute Experimental Pain in Autism Spectrum Disorder), these were conducted to ensure that any differences in avoidant behaviours or facial expressions were not due to differences in pain thresholds. Findings from the heat pain threshold and cold pressor threshold in Experiments 3 and 4, support the findings from earlier QST experiments (Chapter 2. Psychophysical Approach to Pain in Autism Spectrum Disorder, Experiments 1 and 2) and together supports the conclusion that thresholds do not differ in ASD (Fründt et al., 2017; Vaughan et al., 2019). Prior to this thesis much of the work investigating thresholds yielded contradictory findings, either a hypersensitivity (Blakemore et al., 2006; Cascio et al., 2008; Chen et al., 2009; Fan et al., 2014; Riquelme et al., 2016) or no group differences between ASD and controls (Bird et al., 2010; Cascio et al., 2008; Güçlü et al., 2007). Much of this work was methodologically smaller, considering only a single modality, or was not primarily interested

in pain in ASD, and so findings from this thesis extend the knowledge of pain in ASD. Both by its consideration of multiple modalities and its systematic testing of thresholds. This research body had also not considered suprathreshold and by incorporating a cold pressor task (Experiments 1,2,3 and 4) and a measure of heat pain tolerance (Experiments 3 and 4) this thesis methodologically extends the current approaches to investigating pain in ASD (see section 5.4 for a discussion about future directions).

In Experiment 4, the ASD group showed a significantly lower tolerance compared to controls for the cold pressor task, a finding which was not reported in the samples from Experiments 1 and 2, nor found for heat pain tolerance (Experiment 3). In Experiments 1 and 2 the sensory phenomena paradoxical heat sensations and dynamic mechanical allodynia were reported in autistic individuals or high autistic trait severity. Furthermore, mechanical detection threshold was reported at a clinically significant degree of sensory loss for these individuals. The ASD group also showed consistently higher standard deviations across many of the variables, including threshold data, self-report pain intensity and unpleasantness ratings, response times (including latencies, initial response times and response times; Experiment 3), as well as for facial expression data (Experiment 4). These findings support the notion that there may be subgroups within ASD with altered pain response and the high variability could also be in accordance with the complexity and clinical heterogeneity of ASD itself (Lai et al., 2013). For example, recent research has established several homogonous groups each with their own phenotypic presentations of the ASD spectrum criteria (Cohen & Flory, 2019; Mihailov et al., 2020; Wiggins et al., 2017). However, these studies rarely included pain response as part of their clustering analysis because the measures used themselves did not incorporate more specific criteria about pain. It may also account for the lack of consensus in the literature regarding pain sensitivity (Duerden et al., 2015; Fründt et al., 2017; Vaughan, et al., 2019; Williams et al., 2019), especially the anecdotal and

observational work (Cesaroni & Garber, 1991; Elwin et al., 2012; Gillberg & Coleman, 2000; Grandin, 1992; Mahler et al., 2018; Messmer et al., 2008; Militerni et al., 2000; Nader et al., 2004; Rattaz et al., 2013; Tordjman et al., 2009). A particularly clear example from this thesis of the heterogeneity of pain response in ASD can be observed in the individual QST profiles in Experiments 1 and 2. Notably, there was a larger number of QST thresholds that fell outside the normal distribution in the clinically diagnosed ASD group (Experiment 2), and a greater number of ASD individuals were found to show atypical patterns of pain response i.e., their number of thresholds that were at a degree of clinically significant loss or gain was greater than 2. This highlights the importance of extending the heterogeneity of ASD to include pain response, as well as the importance of extending analysis beyond that of typical group differences (see section 5.4 for a discussion of future directions). Such individual analysis as conducted in this thesis, again extends the earlier work which had a greater focus on group differences. However, there was no systematic group differences in peripheral processing, suggesting that the observed insensitivity in the anecdotal evidence may be highlighting those individuals with a sensory processing change and incorrectly this is being generalised as a feature of ASD.

5.1.2 Nociceptive Evoked Cognitive Response

Furthermore, pain response subgroupings of ASD may also extend to an anxiety phenotype (Experiment 3, for further discussion see section 3.4). Importantly, this is the first experiment in the study of ASD and pain to have assessed the evaluation of a painful stimulus by autistic individuals. There was intact associated learning in the ASD group and they also decided to negate the pain to receive a reward comparable to controls and neurotypicals (Claes et al., 2014, 2015, 2016). Even though they were simultaneously more fearful and wished to avoid the painful stimulus to a greater extent than controls (both pain related fear

and avoidance have previously been shown to increase pain sensitivity and exaggerate the pain experience in neurotypical populations [George et al., 2006; Hirsh et al., 2008; Horn et al., 2014; Robinson et al., 2010; Roelofs et al., 2005]). This shows a personal agency in the evaluation of pain that has not been considered elsewhere in the study of pain in ASD. Therefore, it is possible that beyond an anxiety phenotype, there may be more nuance to these subgroupings. For example, where previous research has shown an association between anxiety and pain responses in ASD (Failla et al., 2020; Garcia-Villamisar et al., 2019), participants in Experiment 3 had no differences in pain threshold and tolerance. Failla et al., (2020), reported that participants differed to controls on all subscales of the Pain Anxiety Symptoms Scale, which is a general measure of pain related fear and anxiety. In which participants are asked how frequently they engage in behaviours when in pain. This ambiguity about "pain" may result in participants answering this in relation to very different types of everyday pain, compared to the single item used in Experiment 3 asked directly in connection to the application of a stimulus. The difference in these measures may reflect a difference between state and trait anxiety, in which state anxiety reflects the psychological and physiological reactions directly related to an adverse event, at a specific moment (Saviola et al., 2020), in this case, a pain stimulus, since pain is defined as adverse (International Assosiation for the Study of Pain, 2020). Some evidence also points towards state anxiety leading to increased pain intensity ratings, above and beyond whether participants had high or low trait anxiety (Tang & Gibson, 2005) although this was in neurotypicals. Recent evidence also points towards a more varied presentation of anxiety in ASD, which may or may not align with the specified anxiety disorders (Kerns et al., 2020). Therefore, accounting for both the differences in findings between this experiment and the published research in terms of pain response, as well as this being a potential avenue for consideration for phenotypes of

anxiety in the clustering of pain and ASD traits (see section 5.4 for discussion of future directions).

The existing evidence also had not considered the connection between anxiety and pain from a motivational perspective (Failla et al., 2020; Garcia-Villamisar et al., 2019), instead showing only associations between measures of pain anxiety and observed pain response or self-reported pain ratings. Therefore, Experiment 3 is an is an important step in the study of pain in ASD, in that it considered pain, anxiety and reward, as several demands that occur simultaneously and impact on pain depending on where attention is directed or what evaluation occurs (Botvinick & Braver, 2015; Crombez et al., 1994; Crombez et al., 2005; Crombez, Eccleston, Van Damme, et al., 2012; Eccleston & Crombez, 1999; Van Damme et al., 2008, 2010). While Experiment 3 took place in a controlled setting, this may not be reflective of the true contexts in which pain is occurring or be capturing the true point at which pain becomes too interruptive and so an individual typically seeks help (Hadjistavropoulos, et al., 2011). For example, autistic individuals may experience pain whilst in novel environments that are richer in sensory information, such as the medical setting of a dentist, where there are lights, equipment, noise from equipment and multiple medical staff, such as those used in previous research (Nader et al., 2004; Rattaz et al., 2013). Further, an individual's perception of, and behaviour in these sensory rich environments will naturally vary on a number of levels, including anxiety in relation to novel environments (Gulsrud et al., 2007; Moore, 2015; Vivanti et al., 2018) and they may also be experiencing overload of other sensory modalities (Baum et al., 2015; Marco et al., 2011). There may also be stimming and or a saliency for restrictive repetitive behaviour patterns, in a phenotypically heterogenous way (Elwin et al., 2012, 2013; Masi et al., 2017; Volkmar & Reichow, 2013). As these individual differences in perception and subsequent behaviour have not been captured in the laboratory-controlled settings of Experiment 3, it is unclear how they might

influence pain and pain related behaviour. However, it can be inferred from the results of this thesis that when other motivationally relevant simultaneous demands are not present, the interruptive effects of pain, or the processing of pain, or communication of pain in ASD does not differ compared to controls (see Experiments 1,2,3,4). It is possible that the complexity of the interaction of these factors, and the heterogeneity in which they may be motivational, impact on pain response. This may also account for the differences in findings between this thesis and the anecdotal evidence. Furthermore, evidence shows that avoidance behaviour is influenced by the motivational context (Goubert et al., 2011), and also point to and support the notion of a heterogeneity of ASD, and so this heterogeneity should be considered in terms of the motivational component of all goals, including pain (Vaughan et al., 2019). If a more dynamic and personally relevant motivational view is adopted in future research, which considers the goals and values of the individual, it is likely that the boundaries of motivation and fear-avoidance and pain could be considered (Van Damme & Moore, 2012; see section 5.4 for discussion of future directions).

5.1.3 Communication of Pain

This also points to contextual factors playing a larger role in pain in ASD. In Chapter 4, it was proposed that the social display rules, driven by the social context, dictated and modulated expressions of pain (Robbins & Vandree, 2009; Smoski & Bachorowski, 2003). In particular, that once the researcher was out of sight, the ASD group were unable to gauge the attention of the researcher which encouraged them to be uninhibited in their response (Trevisan et al., 2018), therefore resulting in greater expressive communication. Since ASD is characterised by social impairment (APA, 2013) it may not be surprising that the details of the social environment or perceptions of perceived sociability (or lack thereof), may influence the pain experience, particularly if pain is considered from a social communication

perspective. However, this extends beyond just the expression of pain, manipulating the observer through using partners and strangers has shown that neurotypicals show a decrease in pain ratings when the relationship is closer (Brown et al., 2003; Krahé et al., 2013; Vlaeyen et al., 2009), therefore the social modulation of pain extends to the perception of pain. Furthermore, the effect of threat on verbal and facial expressions of pain, are dependent on social context (Karos, Williams, et al., 2018; Vlaeyen et al., 2009). The aforementioned research (see Krahé et al., 2013 for review), established that close interpersonal relationships reduce pain ratings, where a close partner is thought to act as a safety signal in threatening contexts (Vlaeyen et al., 2009). More recently, Karos et al., (2020), manipulated participant's beliefs about the number of stimuli being delivered, to either be a maximum delivery of stimuli (1-10) or a minimum (10-20) when 10 stimuli were delivered. Findings show that when experiencing a noxious stimulus, delivered by a close partner, neurotypicals showed less intense facial expressions and had higher pain ratings, highlighting that the degree to which the intentions of a partner can be determined can impact on participants painful experiences. However, this body of work was conducted in neurotypical participants and does not consider those with disorders whose core features are social communication deficits. It is plausible that when in a less complex social environment, such as the lab-based experiments in this thesis, there is less social modulation of pain in ASD. This leads to the possibility that complex social environments, such as medical appointments e.g., dental appointments (Nader et al., 2004; Rattaz et al., 2013; Tordjman et al., 2009), or indeed just a family setting when someone has experienced pain, there is a social modulation of pain. This could potentially occur because autistic individuals are trying to navigate the social environments through their social communication difficulties. Furthermore, this social modulation of pain might only occur when there are sufficient social skills, or where deficits in social communication are less severe. For example, the participants from this thesis were

4431 those with greater socio-communicative abilities, who were able to express their pain whether
4432 it be facially or verbally, in comparison to those described in the anecdotal evidence whose
4433 social deficits may be more severe. In these individuals, social modulation of pain may not
4434 be present because of the severity of the deficits. Additionally, it is possible that the
4435 modulation is greater for facial expressions of pain than pain ratings, which could account for
4436 the differences in findings between lab-based studies such as this thesis, and those more
4437 ecologically conducted. Future research should attempt to tease apart the influence of social
4438 context and interpersonal relationships in conjunction with social communication deficits in
4439 ASD (see section 5.4 for a discussion of future directions).

4440 **5.2 General Discussion**

4441 It is also possible to consider findings from this thesis, from a developmental
4442 perspective as such changes are apparent in the experience and expression of pain. As
4443 individuals age, they acquire the capacity to understand painful experiences and consciously
4444 engage in self or social control (Pincus & Morley, 2001). Help-seeking is voluntary or
4445 effortful (Hadjistavropoulos, et al., 2011) and pain communication becomes more deliberate
4446 and language more complex (Stanford et al., 2005) as individuals age, even though the non-
4447 verbal components of pain cannot be wholly suppressed (Craig et al., 1993), contrasting this
4448 with children, where the behaviour can be thought of as stereotyped, or reflexive. For
4449 example, neonates and children display clear signs of painful distress by crying, to alert
4450 caretakes to their needs and to initiate care (Craig et al., 1993; Fitzgerald, 1991).
4451 Additionally, observational learning in childhood influence both observable expression of
4452 pain as well as the subjective experience (Craig & Weiss, 1971; Goodman & McGrath, 2003;
4453 Goubert et al., 2011; Patrick et al., 1986). As we age therefore, there is maturation of the
4454 biological substrates serving pain, emotion, cognition, language, and behavioural competence

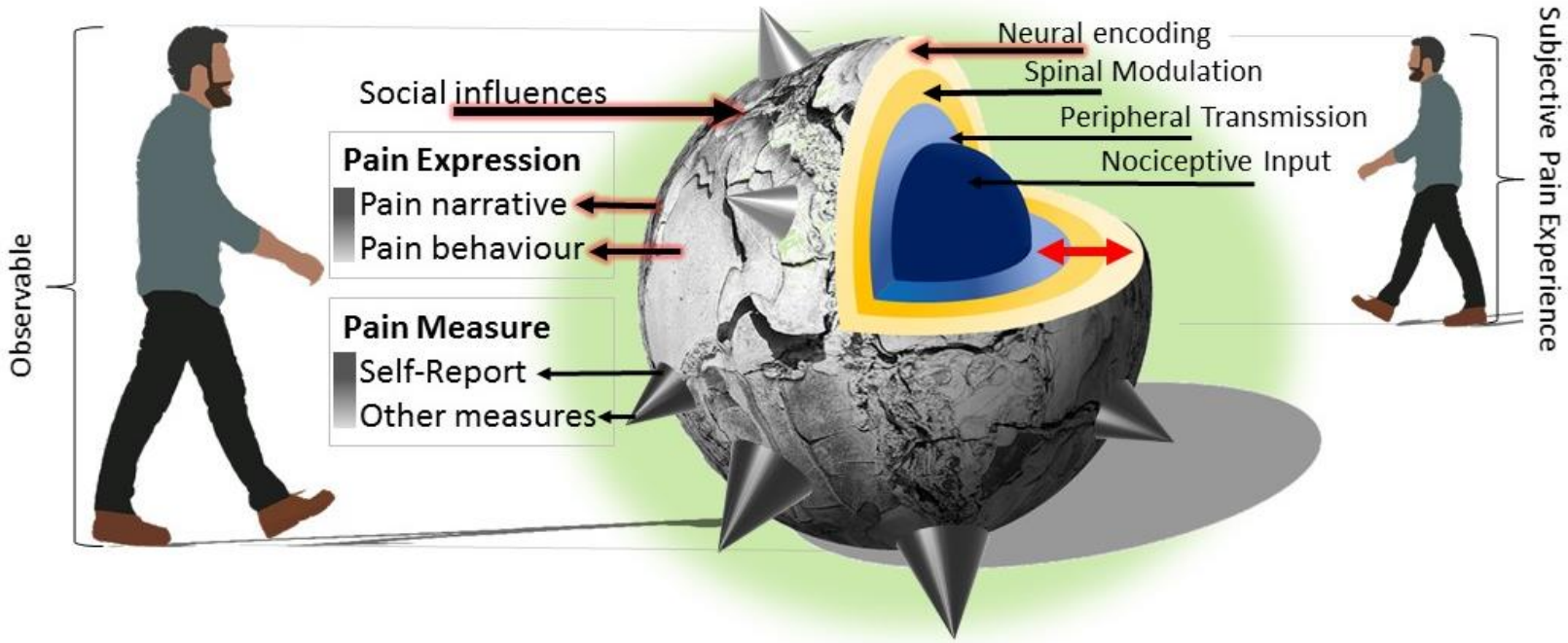
(Backonja et al., 2013; Brewer et al., 2020; Hatfield, 2014; Levy et al., 2018; Maier et al., 2010; Simons & Tibboel, 2006). Therefore, the pain experience must require progressive cognitive development and acquisition of social communication skills. Developmental delay, however, is a significant lag in reaching the typical childhood milestones in language, cognition, social, and emotional milestones which are typically reached at different stages in childhood development (Stabel et al., 2013). In ASD, some of these milestones may not be reached at all and some may be reached later. Since participants reported here were able to communicate their pain facially (Chapter 4), provide self-report of intensity and unpleasantness of the stimuli (All Chapters), and provide threshold data (Chapter 2), there was evidence of sufficient cognitive development, cognitive progression, and acquisition of social communication skills to both understand pain and to communicate their pain experience (Cholemkery et al., 2016; Szatmari et al., 1995; Uljarević et al., 2020). This is despite cognitive development, progression and social communication skills being considered atypical for a diagnosis of ASD (APA, 2013; Bishop-Fitzpatrick et al., 2017; Delehanty et al., 2018). In contrast, those samples with severe socio-communicative disabilities and developmental delay may experience a delay in the acquisition of pain specific communication (Nader et al., 2004; Rattaz et al., 2013), and/or the capacity to understand painful experiences. Therefore, it is possible that the pain behaviour of those individuals retains the reflexive stereotyped nature of younger children. It may also be that the capacity to understand painful experiences that results in the self or social control that is evident in older children and adults, may not have fully matured. However, no research to date has investigated progressive cognitive development and pain communication or understanding of pain experience in ASD (see section 5.4 for a discussion of future directions).

Together these findings and the proposed explanations suggest that the earlier conceptual model can be adapted for ASD to reflect that there is likely greater interplay

between the outermost layer, representing pain behaviour, and the environment, including observers (reflected by the deeper shade of green for the environment and the red hazed wider arrows for pain expression). It is also likely that social influences play a larger role and that the interaction between these and cognitive-affective components in the neural coding section of the model may be greater (indicated by thicker red hazed arrows). Since there were some sensory phenomena that does not typically occur in healthy individual without neuropathy, it is likely that the spinal level is also an area of interest, however since this occurred in a limited number of individuals, the prominence of the change to the model is less. Rather than aspects being absent, data suggests differences in these areas in ASD. Therefore, the further adapted Integrated Multimodal Model of Pain (see figure 30) highlights where these differences are likely to occur in the pain experience for autistic individuals.

Figure 30.

The Loeser/Wideman Integrated Multimodal Model of Pain for Autism (The IMMP).



Note: This 3-dimensional view emphasizes the subjective pain experience and the observable person perspectives. The core of the model and the subterranean layers highlight the internal unobservable mechanisms that are involved in the pain experience. Nociception is at the core to reflect that nociception typically results in pain, and the peripheral, spinal, and neural mechanisms involved. However, since pain can occur without nociception, and that there is also a top-down modulation of pain, the red arrow on the subterranean layers, indicates that there are bi-directional processes occurring through these layers. The neural level represents the motivational-affective, cognitive evaluative and sensory discriminative functioning. This 3D view also emphasizes how pain experience is a function of the whole person, who is influenced by environmental and contextual factors (indicated by the green haze) including social influences (indicated by the textured cracked surface, cracks indicating that social, environmental, and contextual factors seep through to the internal). The textured uneven surface of pain expression represents the collection of words and behaviours that any individual may use to express pain. This contrasts with the smooth surface of pain measures (cones), which require expressions of pain to be translated into metrics. Cone size represents the relative ability of different pain measures to quantify different aspects of pain expression; measures with relatively larger cones indicate that they address a broader scope of pain expression. Gradients are used to depict the intimate link between the pain narrative and pain behaviour. This model integrates aspects from both Loeser (1980) and Wideman et al., (2019) models into one comprehensive biopsychosocial model. All images, with the exception of the walking man (creative commons licencing: https://cdn.pixabay.com/photo/2017/08/17/15/32/walking-2651721_640.png), belong to the author of this thesis, having been created, edited and adapted by the author (SV) for the purposes of generating this diagram.

5.3 Limitations

There are several limitations that are relevant to each individual experiment (see 2A.4, 2B.4, 3.4 and 4.4), however, there are also some overarching limitations that warrant further discussion. The first of which is that this thesis did not define sub-groups of ASD, and samples were entirely comprised of those with greater socio-communicative abilities. The samples, therefore, did not reflect the entire ASD spectrum, with those with severe socio-communicative disabilities not included. Nor did it subgroup ASD characteristics. This recruitment bias is unfortunately frequent in research utilising similar methodologies (Cascio et al., 2008; Duerden et al., 2015; Fründt et al., 2017; Vaughan et al., 2019) or where a self-report of pain is required. However, this is common within the literature, particularly complex experimental studies as there is no ethical and safe methodology that would allow investigation of the same aspects of pain, as have been conducted here, in those with severe socio-communicative disabilities. The priority above the attainment of knowledge is the well-being of the individual. Though the goal of understanding pain in the ASD spectrum is to improve their well-being, especially as these individuals, are potentially more likely to experience altered pain (as based on anecdotal evidence). Translational work, specifically around improving treatment and care of pain in ASD will be a benefit.

The overarching limitation, however, was sample size and is a consistent theme in such studies. Sample sizes were small resulting in the risk of type II errors, weakening our ability to provide results that can support or refute those currently reported. One area that may resolve this is working more closely with ASD services or hospitals. Recent research that has improved on sample sizes, appears to have been successful in this recruitment method (Dubois et al., 2020; Garcia-Villamisar et al., 2019; Williams et al., 2019), although this research was conducted outside of the UK and in the UK such services are resource

deprived which may limit the ability to support research. This is an area that I have been reflecting upon recently. Particularly, when a global pandemic means a redistribution of health resources in an already resource deprived health system. One area which could be used in a greater capacity for data collection is that of social media. This may also have the benefits of reaching a wider ASD population as research has shown that social media usage in ASD is high. In one study, 79% of ASD participants used social networking sites (Mazurek, 2013) with up to five hours a day spent online (Kuo et al., 2014). One systematic review also showed that social media as a tool for study recruitment helped to target hard-to-reach populations (Whitaker et al., 2017). However, social media recruitment has been linked to greater staff time and average hourly cost (Moreno et al., 2017). This coincides with my own personal experience with social media, in that those accounts with the greatest following, and therefore more likely to have a greater chance at reaching individuals, require greater investment of time. For future research, social media recruitment, such as sponsored links, should be considered with such recruitment costs factored into grant applications.

A further limitation shown in Experiments 3 and 4, was that the stimulus temperatures were predefined for all participants. In Experiment 3, the stimulus intensity was set at 52◦C, and in Experiment 4 this was 41◦C (non-painful), 44◦C (moderately painful) and 47◦C (very painful). These pre-defined temperatures were driven by ethical considerations which required lower temperatures than initially proposed. In particular, the very painful stimulus from Experiment 3 is lower than other published research using the fixed stimulus intensity methodology (Failla et al., 2018; Kunz et al., 2008; Lautenbacher et al., 2017; Thibodeau et al., 2013). Moreover, there were 11 participants whose heat pain threshold was higher than the moderately painful stimuli, as well as 12 participants whose tolerance was also higher than the very-painful stimuli, suggesting that participants may not have felt the stimulus as either moderately or very-painful, and although stimulus intensities were designed to move in

an increasing slope from non-painful to moderately painful and then very painful, that some participants may have instead experienced two non-painful and one moderately painful stimulus. There is also some evidence that fixed intensities are perceived as painful by some participants but not others (Strulov et al., 2007) supporting the threshold and tolerance data from these experiments. Temperatures adopted here therefore, could be problematic in that they may not have adequately reached a painful level. One alternative is to focus on pain ratings of a particular intensity, or to individually determine the temperature at which the stimulus is delivered using a search protocol that gives a particular instruction such as, "adjust this temperature until it is moderately/very painful" (Moore et al., 2013). However, this is inherently problematic for the method where the focus is on determining either facial expressions or avoidance behaviour where conditions are similar across participants. For example, participants may have deliberately chosen lower temperatures to avoid feeling pain (Rolke, Baron, et al., 2006) which would add additional variability to the data. Furthermore, the intensity ratings from both Experiments 3 and 4 inidcated that the stimuli were perceived in the according order, for example non-painful was rated the least painful and the very painful was rated the most painful. Therefore, although in terms of physical intensity the temperatures may seem problematic, the subjective ratings highlight a perceived intensity that showed participants experienced pain to the desired differing degrees required for both methodologies.

5.4 Future Directions

A first step for future research, would be to expand upon and focus on the measure of tolerance. This is particularly important due to there being both reported differences between ASD group and controls in some samples but not others, as well as individual difference and no group level differences in ASD compared to controls for thresholds. Tolerance itself, may

be more representative of clinical everyday pain, not only because its duration is longer, much like painful experiences, such as headache etc., but because it includes cognitive factors, such as motivation and endurance (Chapman et al., 1985; Cleeland, Nakamura, Howland, et al., 1996; Cleeland, Nakamura, Mendoza, et al., 1996). Additionally, the induction techniques used for tolerance were limited to the temperature modality, with other modalities not considered. This contrasted with the multimodal approach taken when utilising QST, and so one lesson would be to continue with multimodality testing, as this too is more representative of the types of pain experienced every day (Backonja et al., 2013; Rolke, Baron, et al., 2006).

Additionally, mechanical detection threshold was the only test for which clinically relevant degrees of sensory loss in ASD were reported, therefore, examining the mechanical modality, further would be a useful addition. For mechanical tolerance computerised pressure algometry could be utilised because it is difficult to maintain application rates over test periods in manual algometry (Jensen et al., 1986; Kosek & Lundberg, 2003; Melia et al., 2015). Computerised algometry may also provide the opportunity to measure the course of the stimulation rather than the maximum force reached in manual algometry, particularly if this is paired with a threshold to tolerance curve, so that the reporting of pain across a duration from first detection to unable to tolerate can be measured. Providing richer data points to determine where in this process differences occur that might account for the observed differences in the anecdotal accounts. Although aspects of tolerance were measured throughout this thesis it was done so as the highest stimulation intensity tolerated, which is still a single point measure. Sustained pain, a characteristic of clinical pain, may be replicated in experimental studies (Failla et al., 2018, 2020; Lee et al., 2021) and should be considered within protocols measuring tolerance. For example, there may be differences between the point at which an acute pain stimulation is experienced as being intolerable and

the point at which sustained pain is intolerable and help is sought (Hadjistavropoulos et al., 2004). The use of Capsaicin could be considered as it may also provide a closer representation of clinical pain, one that induces deep visceral pain and an inflammatory reaction (Campbell, 1983; O'Neill et al., 2012; Petersen-Felix & Arendt-Nielsen, 2002), and has yet not been adopted.

One of the most important considerations for future research generated by the findings from this thesis, and the proposed explanations discussed previous, is the importance of establishing if there is a sensory subtype in ASD and if there are clusters of ASD subtypes that are related to altered pain response. Future research should adopt analyses that emphasise the study of the individual or clusters. Traditional research methodologies can obscure underlying processes by shrouding rich individual data with group data aggregation procedures (O'Connor, 1990). A distinctive feature of a multi-level modelling approach is the focus on intraindividual variability in the behavioural and physiological processes of an organism, for example, highlighting the variability in social features of ASD, social context and pain. In multilevel models inter- and intra-individual variability can be simultaneously estimated. Therefore, helping to deal with data that may have a clustered structure. Moreover, within-group variance (typically treated as error in traditional experimental psychology) is also investigated since it contains a wealth of relevant information (Cronbach, 1957). Thus, it may address the limitations, and account for the individual variance observed throughout the findings of this thesis (Wright & London, 2009). Recently published data has attempted to do this using hierarchical multiple regression to assess group difference whilst controlling for age, sex, counterbalance order and diagnosis (Williams et al., 2019). Williams et al's findings show no differences between those with ASD and controls, and modest group differences in intra-individual variability, supporting the findings from this thesis. This analysis also yielded important factors, such as lower IQ, male sex, and higher intra-

individual variability as the most significant predictors of elevated detection thresholds, highlighting the utility of this analytical approach. Others have also continued to recognise this variability (Dubois et al., 2020; Garcia-Villamisar et al., 2019). There are a range of clustering analyses that could be adopted, for example, Agglomerative Clustering would provide the benefit of identifying clusters of criteria, whilst confirming their belonging to the larger cluster of ASD itself. The use of such clustering analyses might help in confirming diagnoses based on criteria, as well as highlighting the clustering and heterogeneity within (Bitsika & Sharpley, 2015). However, much of this work has been predicated on using multiple measures of ASD. This approach may be largely exhaustive for participants, particularly if this is paired with complex pain induction methods in experimental designs. Therefore, consideration of participants is important here too. There appears to be further consensus that subgrouping ASD and pain symptoms is of utmost importance. Personally, my formal education is largely based around this group aggregation analytical approach. Prior to this, my training in Psychology and Health Psychology, largely looked at general population trends and large data sets which were non-experimental. This PhD challenged this approach in that it attempted to step beyond this by considering complex patterns at an individual level. As findings go further to suggest intra-individual differences, I must continue to expand my understanding of multilevel modelling, to be able to generate future research with an analytical approach that may be better suited to addressing some of the questions around pain in ASD that remain.

Furthermore, research should extend to identify if there is an anxiety related subtype (as discussed in section 5.2 above) by incorporating both state and trait anxiety factors into the cluster analysis mentioned previously. As done in Experiment 3, measuring pain related anxiety as experienced in relation to a stimulus would be useful as a representation of stimulus specific state anxiety, and would differentiate pain related anxiety that is general

about painful experiences providing greater control. Manipulations could be used as a tool for state anxiety, where different groups experience, or conditions contain, different cues related to stimulus onset. These approaches would aid in determining which state or trait anxiety factors operate upon pain response in ASD above and beyond associations (Edens & Gil, 1995).

This individual approach to understanding pain in ASD should also extend to understanding motivation and avoidance behaviour. As previously discussed, there are many goals and competing demands that may be present simultaneous to pain, some of which may be specific to ASD symptomology. A first step to understanding these associations in more detail and at an individual level may be to ask participants which goals they have experienced during painful episodes and which ones had greater saliency or motivational quality (Zaman et al., 2018), and importantly why. This may help to more closely understand which factors to investigate in terms of attenuation of pain, or when pain becomes the more salient goal. A blanket reward for all participants, as used in Experiment 3 and that is typically used in reward-goal attenuation research, may be differentially motivational and so the personal level at which pain becomes motivational and can no longer be attenuated is missed. However, this requires a greater knowledge of a qualitative approach that I currently hold particularly to uphold the same rigour as applied in this thesis. Exploring qualitative methodologies could be the next step in preparing to expand upon these ideas. That is not to discount a quantitative approach to individual motivations. For example, it is acknowledged that the Pavlovian fear conditioning procedure may lack ecological validity, and that work conducted since the data collection of this thesis, that adds a cost to the avoidance, would be a quantitative methodology to consider in the future (Glogan et al., 2020). Specifically, alongside the reward the actual expended cost could be related to a movement, as utilised by Glogan et al., (2020). This work should also consider the context in which pain and the

motivation to avoid this occurs, to a greater extent than has been currently, particularly in light of a findings that point towards a social modulation of pain.

The connection between social deficits, the social context and the impact on pain experience and its expression should be considered. In particular, the effects on pain by the environment itself, including perceived threat, motivations and goals and interferences could be avenues for consideration (Krahé et al., 2013). Furthermore, since much of the research in neurotypicals samples has considered that social partners can act as a safety net in threatening contexts, and that autistic individuals may struggle to navigate interpersonal relationships and complex social settings, internal models of relating to other people and social deficits impact on pain experience should be considered. This would require experimental manipulation, possibly across a multi-study approach, where the partner and the environment are manipulated, whilst measuring the saliency towards these. For example, safety and threat could be manipulated by having clear intentions from different observers, or by having single or multiple observers in the room, or indeed adopting the threat manipulation used by (Karos et al., 2020). Determining the connection between ASD and the social modulation of pain would be a clear step with important implications for pain communication in a range of social settings. However, attempting to consider how this could be done in those across the entire spectrum would be important too. By its nature, such experimental work would again recruit those with adequate socio-communicative abilities and so would still be limited by not incorporating the whole ASD spectrum, particularly when it is heterogenous. It may also require the adoption of more advanced analytical techniques, particularly if it is to model the connection between ASD factors, social factors, and pain. This also highlights an important lesson learnt through this PhD, in the importance of obtaining self-report measures of intensity and unpleasantness alongside stimulus intensities, or to use these as a manipulation check of the chosen methodology.

There are several avenues to reflect upon and consider in reference to future directions in terms of researching cognitive progression, ASD and pain experiences. Presented here are initial thoughts and reflections. Firstly, a consideration of an operationalised definition of cognitive progression would be needed. One approach may be to consider this from a developmental milestone's perspective, particularly, as ASD is a neurodevelopmental disorder associated with developmental delay. Secondly, although it is connected to the definition, a metric of progression is needed. Published guidelines that include lists of individual milestones could be used. Cohort studies in the UK, Finland and Denmark report correlations between the age of attainment of these milestones and a range of adult outcomes (Flensborg-Madsen & Mortensen, 2018; Murray et al., 2007; Stochl et al., 2019), suggesting their utility as a metric. These guidelines could be used in a categorical system to show whether they were attained or delayed or not attained at all. However, since the aim is to establish progression, it would be imperative to provide indexes of change, rather than just a categorical 'achieved' or 'not achieved'. To address this a timepoint measure could be taken for if milestones were delayed, providing more rich data points for analyses. Furthermore, there has been normative data published in America, which could act as a threshold for which attainment is measured (Sheldrick et al., 2019). For example, the last of the cognitive and communication milestones are typically achieved at 60 months. Since this is based on typically developing individuals if such a metric were adopted, because those with ASD may experience delay, an analytical procedure would be needed to account for this. One way to deal with developmental delay in relation to the normative values would be to add a value of one SD above their age which would clearly place the milestone in the delayed range without introducing non-uniformity in that data (Arnett et al., 2020).

One critique of developmental milestones is that is does not account for continuous changes in mental capacity (Lourenço, 2016). Additionally, there may not be a single

developmental pathway that is completed in early childhood. There may be different developmental trajectories and careful consideration of this is needed (Craik & Bialystok, 2006; Karmiloff-Smith, 2006). This seems more in line with what is meant by cognitive progression as discussed earlier (see section 5.2). Additionally, recent research has begun to take a lifelong approach to development. Pairing this with the age related maturation of the biological substrates serving pain, emotion, cognition, language, and behavioural competence (Backonja et al., 2013; Brewer et al., 2020; Hatfield, 2014; Magerl et al., 1998; Rolke, Baron, et al., 2006; Simons & Tibboel, 2006), it might be useful to expand our definition of progression beyond the limits of current developmental milestones literature. Therefore, it may be beneficial to further consider other avenues that could also act as measures of cognitive progression. For example, executive functioning allows for successful adaption to complex environmental conditions, and broad dysfunction in ASD has been reported suggesting this as a useful avenue for consideration (Demetriou et al., 2018; Zwick, 2017). The domains of executive function being measured would define the tests that might be utilised (de Faria et al., 2015), such as the Wisconsin Card Sorting Test which assess mental flexibility.

Thirdly, in attempting to understand cognitive progression it may be reasonable to consider longitudinal research designs, in that these studies employ continuous or repeated measures to follow individuals over a prolonged period (Caruana et al., 2015). Additionally, longitudinal research designs lend themselves to analysing change over time for a group or for individuals. On reflection, this appears a warranted consideration when the aim would be to understand cognitive progression and its impact on pain experience. Additionally, as findings from this thesis indicated that there needs to be greater consideration of intra-individual variability, the analysis of individuals change over time could help form a more precise and dynamic picture (Georgiades et al., 2017). A number of studies have used

longitudinal designs when investigating cognition, language and social and behavioural outcomes (Magiati et al., 2007). However, many of these are conducted outside of the UK and frequently they are linked with studies conducted either in conjunction with hospitals or specific ASD hospital services. Considering the aforementioned discussion around sample size (see section 5.3) it may take some time to establish any such connections in order to conduct such longitudinal research. Longitudinal designs are also costly, time consuming and complex (Telzer et al., 2018), and subject attrition rates high, which was also the case in this thesis, with many participants showing initial interest but not booking to attend lab sessions. One alternative for examining developmental trajectories is a cohort sequential design, in which multiple measures are taken over a defined period from multiple groups of different ages, who are enrolled at various time points in the study (Prinzie & Onghena, 2014). These are powerful designs, because they allow for comparisons of changes and stability with age over time as well as group comparisons. This avenue of research and future directions requires a more careful consideration and deeper investigation and knowledge acquisition to fully formulate operational research studies. The same personal reflections made in reference to understanding more complex statistical analyses are relevant here. Additionally, careful planning of each stage of this is needed. No single study could address these connections in its entirety and so it is a body of research work that would extend across several years. However, in understanding the connection with cognitive progression, ASD and pain experience (namely pain response and understanding), it may be possible to enhance single cognitive processes in a targeted manner to promote improved coherence in order to express pain or to invoke help (Zwick, 2017). For example, in understanding problems with pain language acquisition and comprehension as well as differences in pain language could help develop a taxonomy of pain that is specific for ASD or help in designing interventions

around the acquisition of pain language. Communicating this taxonomy to HCPS then can assist in more appropriate support for those with ASD.

5.5 Implications/Conclusion

The most important implication from the findings of this thesis is that the absence of the ability to feel pain, as suggested in the DSM-5 (APA, 2013)*, is not a defining feature of ASD.* Therefore, if a procedure or experience is considered to be painful, then it should be treated as such in ASD. For example, Rattaz et al., (2013) reported that there were fewer autistic individuals receiving anaesthetic during a painful dental procedure, compared to controls. It could be assumed that this is based on the difficulties of understanding or of diagnosing pain, or that autistic individuals can experience distress to novel stimuli (Gulsrud et al., 2007). However, there is inherent risk in undermining pain experiences and therefore it would be pertinent to consider that the absence of pain in ASD is not a defining feature of ASD and therefore should not be treated as such.

Findings also point to greater intra-individual differences in ASD, therefore, it is important to assess how autistic individuals manifest pain and anxiety (Benich et al., 2018; Taghizadeh et al., 2015). Findings also point towards there being important nuances in the facial expression of pain in ASD. As pain communication in observers is particularly reliant on facial expressions this is an important aspect to be considered (Craig & Patrick, 1985; Kunz et al., 2019; Prkachin, 2009). None of the validated assessment tools used for measuring pain in clinical settings incorporate individual pain behaviours, or ASD specific responses. The facial expressions of pain are also currently biased as they are solely based on those considered healthy. Additionally, they also do not work on change, rather as a static measure of the behaviours that is time locked. This is problematic, in that the findings from this thesis point towards a potential explanation of a social modulation of pain, and so

understanding historical behaviours related to pain, as well as a change in behaviour appears important. This also highlights a second flaw with such measures. If there is a social modulation of pain, wherein complex social environments lead to a reduction in what is understood to be a painful behaviour (such as the absence of a grimace), scales higher scores represent higher pain may not be suitable in ASD. In this instance, a change score would be beneficial, although more work is required to understand if there is a social modulation of pain and what the mechanisms are, as well as establishing more ASD appropriate validated measures.

Despite there being no research to establish whether there exists a social modulation of pain in ASD, or what the causal or mechanistic aspects of this may be, a clear recommendation would be for individuals to be more direct and literal in communicating their intentions when interacting with autistic individuals who may be experiencing pain. For example, health care professionals (HCPS) could clearly communicate their roles to allow autistic individuals one less instance of social navigation. This may facilitate rapport building and communication particularly when this relationship may involve pain or require pain to be communicated, such as in a GP surgery. In typical medical circumstances, a clear line of sight is created between patient and HCPS, however, findings from this thesis demonstrated that autistic individuals may better communicate their pain when they are not directly observed or perceive that they are not being directly observed (the researcher was sat behind the participants in this thesis and results highlighted no group level differences in pain response). HCPS may therefore want to reflect on how communication is conducted between themselves and those autistic individuals. A person-centred approach is most preferable, where patients would be asked which is most suitable for them. However, other alternatives may be beneficial, such as avoiding direct facing seating arrangements, or instead utilising digital communication or telephone.

In conclusion, this thesis investigated pain in ASD and aimed to expand our understanding of where in the pain process differences occur that could account for the altered behaviours observed in the anecdotal evidence. Various aspects of the pain experience were investigated using robust psychophysical pain induction methods. Findings showed there was no observable consistent QST pattern of difference in relation to autistic trait severity or clinically diagnosed ASD. The ASD groups fear avoidance and pain motivation processing are no different to controls. Painful facial expressions for cold and hot thermal stimuli are similar between the ASD group and controls, although there were important nuances in the expression. The biggest implication from these findings, and for emphasis again, *is that the absence of the ability to feel pain, as suggested in the DSM-5* (APA, 2013)*, is not a defining feature of ASD.* Future research should focus on utilising more complex analyses, such as clustering, in order to account for the heterogeneity observed in the findings from this thesis. Paired with this consideration of the social deficits in relation to social context and pain experience should be considered with specific investigations aiming to establish if there is a social modulation of pain in ASD.

References

Aarts, A. A., Anderson, J. E., Anderson, C. J., Attridge, P. R., Attwood, A., Axt, J., Babel, M., Bahník, Š., Baranski, E., Barnett-Cowan, M., Bartmess, E., Beer, J., Bell, R., Bentley, H., Beyan, L., Binion, G., Borsboom, D., Bosch, A., Bosco, F. A., … Zuni, K. (2015). Estimating the reproducibility of psychological science. *Science*, *349*(6251), aac4716–aac4716. https://doi.org/10.1126/science.aac4716

Accornero, N., Bini, G., Lenzi, G. L., & Manfredi, M. (1977). Selective Activation of peripheral nerve fibre groups of different diameter by triangular shaped stimulus pulses. *The Journal of Physiology*, *273*(3), 539–560. https://doi.org/10.1113/jphysiol.1977.sp012109

Amir, R., & Devor, M. (2003). Electrical Excitability of the Soma of Sensory Neurons Is Required for Spike Invasion of the Soma, but Not for Through-Conduction. *Biophysical Journal*, *84*(4), 2181. https://doi.org/10.1016/S0006-3495(03)75024-3

APA. (2013). Diagnostic and statistical manual of mental disorders: DSM-5^{TM}, 5th ed. In *Diagnostic and statistical manual of mental disorders: DSM-5^{TM}, 5th ed.* American Psychiatric Publishing, Inc. https://doi.org/10.1176/appi.books.9780890425596

Apkarian, A. V., Bushnell, M. C., & Schweinhardt, P. (2013). Representation of Pain in the Brain. In S. B. McMahon, M. Koltzenburg, I. Tracey, & D. C. Turk (Eds.), *Wall and Melzack's Textbook of Pain* (6th Editio, pp. 111–128). Elsevier.

Arnett, A. B., Beighley, J. S., Kurtz-Nelson, E. C., Hoekzema, K., Wang, T., Bernier, R. A., & Eichler, E. E. (2020). Developmental Predictors of Cognitive and Adaptive Outcomes in Genetic Subtypes of Autism Spectrum Disorder. *Autism Research*, *13*(10), 1659–

1669. https://doi.org/10.1002/aur.2385

Asperger, H. (1944). Die “Autistischen pschopathen” im kindesalter. *European Archives of Psychiatry and Clinical Neuroscience.*, *117*(1), 76–136. http://beingapart.blogsport.eu/files/2010/10/Asperger1943.pdf

Atlas, L. Y., Bolger, N., Lindquist, M. A., & Wager, T. D. (2010). Brain mediators of predictive cue effects on perceived pain. *Journal of Neuroscience*, *30*(39), 12964–12977. https://doi.org/10.1523/JNEUROSCI.0057-10.2010

Backes, W. H., Mess, W. H., Van Kranen-Mastenbroek, V., & Reulen, J. P. H. (2000). Somatosensory cortex responses to median nerve stimulation: fMRI effects of current amplitude and selective attention. *Clinical Neurophysiology*, *111*(10), 1738–1744. https://doi.org/10.1016/S1388-2457(00)00420-X

Backonja, M. “Misha,” Attal, N., Baron, R., Bouhassira, D., Drangholt, M., Dyck, P. J., Edwards, R. R., Freeman, R., Gracely, R., Haanpaa, M. H., Hansson, P., Hatem, S. M., Krumova, E. K., Jensen, T. S., Maier, C., Mick, G., Rice, A. S., Rolke, R., Treede, R.-D., … Ziegler, D. (2013). Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain*, *154*(9), 1807–1819. https://doi.org/10.1016/J.PAIN.2013.05.047

Baeza-Velasco, C., Cohen, D., Hamonet, C., Vlamynck, E., Diaz, L., Cravero, C., Cappe, E., & Guinchat, V. (2018). Autism, Joint Hypermobility-Related Disorders and Pain. *Frontiers in Psychiatry*, *9*, 656. https://www.frontiersin.org/article/10.3389/fpsyt.2018.00656

Bagby, R. M., Taylor, G. J., & Parker, J. D. A. (1994). The twenty-item Toronto Alexithymia scale-II. Convergent, discriminant, and concurrent validity. *Journal of Psychosomatic*

Research, *38*(1), 33–40. https://doi.org/10.1016/0022-3999(94)90006-X

Baisch, B., Cai, S., Li, Z., & Pinheiro, V. (2017). Reaction Time of Children with and without Autistic Spectrum Disorders. *Open Journal of Medical Psychology*, *06*(02), 166–178. https://doi.org/10.4236/ojmp.2017.62014

Bandstra, N. F., Johnson, S. A., Filliter, J. H., & Chambers, C. T. (2012). Self-reported and parent-reported pain for common painful events in high-functioning children and adolescents with autism spectrum disorder. *The Clinical Journal of Pain*, *28*(8), 715–721. https://doi.org/10.1097/AJP.0b013e318243ecf6

Baranek, G. T. (2002). Efficacy of Sensory and Motor Interventions for Children with Autism. *Journal of Autism and Developmental Disorders*, *32*(5), 397–422. https://doi.org/10.1023/A:1020541906063

Baranek, G. T., & Berkson, G. (1994). Tactile defensiveness in children with developmental disabilities: Responsiveness and habituation. *Journal of Autism and Developmental Disorders*, *24*(4), 457–471. https://doi.org/10.1007/BF02172128

Baranek, G. T., Foster, L. G., & Berkson, G. (1997). Sensory Defensiveness in Persons with Developmental Disabilities. *The Occupational Therapy Journal of Research*, *17*(3), 173–185. https://doi.org/10.1177/153944929701700302

Baron-Cohen, S., Wheelwright, S., & Jolliffe, T. (1997). Is there a "language of the eyes"? Evidence from normal adults, and adults with autism or Asperger Syndrome. *Visual Cognition*, *4*(3), 311–331. https://doi.org/10.1080/713756761

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning

Autism, Malesand Females, Scientists and Mathematicians. *Journal of Autism and Developmental Disorders*, *31*(1), 5–17. https://doi.org/10.1023/A:1005653411471

Bartlett, M. S. (1947). The Use of Transformations. *Biometrics*, *3*(1), 39. https://doi.org/10.2307/3001536

Basbaum, A. I., & Jessell, T. (2000). The Perception of Pain. In E. R. Kandel, J. H. Schwartz, & T. M. Jessell (Eds.), *Principles of Neural Science* (4th ed.). New York: Appleton and Lange.

Basbaum, Allan I, Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and molecular mechanisms of pain. *Cell*, *139*(2), 267–284. https://doi.org/10.1016/j.cell.2009.09.028

Bauch, E. M., Andreou, C., Rausch, V. H., & Bunzeck, N. (2017). Neural Habituation to Painful Stimuli Is Modulated by Dopamine: Evidence from a Pharmacological fMRI Study. *Frontiers in Human Neuroscience*, *11*, 630. https://doi.org/10.3389/fnhum.2017.00630

Baum, S. H., Stevenson, R. A., & Wallace, M. T. (2015). Behavioral, perceptual, and neural alterations in sensory and multisensory function in autism spectrum disorder. *Progress in Neurobiology*, *134*, 140–160. https://doi.org/10.1016/J.PNEUROBIO.2015.09.007

Beall, P. M., Moody, E. J., McIntosh, D. N., Hepburn, S. L., & Reed, C. L. (2008). Rapid facial reactions to emotional facial expressions in typically developing children and children with autism spectrum disorder. *Journal of Experimental Child Psychology*, *101*(3), 206–223. https://doi.org/10.1016/j.jecp.2008.04.004

Bell, D. C., & Bell, L. G. (1989). Micro and macro measurement of family systems concepts. *Journal of Family Psychology*, *3*(2), 137–157. https://doi.org/10.1037/h0080530

Bemporad, J. R. (1979). Adult recollections of a formerly autistic child. *Journal of Autism and Developmental Disorders*, *9*(2), 179–197. https://doi.org/10.1007/BF01531533

Ben-Sasson, A., Hen, L., Fluss, R., Cermak, S. A., Engel-Yeger, B., & Gal, E. (2009). A meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *39*(1), 1–11. https://doi.org/10.1007/s10803-008-0593-3

Benedetti, F., Lanotte, M., Lopiano, L., & Colloca, L. (2007). When words are painful: Unraveling the mechanisms of the nocebo effect. *Neuroscience*, *147*(2), 260–271. Pergamon. https://doi.org/10.1016/j.neuroscience.2007.02.020

Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., & Rainero, I. (2003). Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *Journal of Neuroscience*, *23*(10), 4315–4323. https://doi.org/10.1523/jneurosci.23-10-04315.2003

Benich, S., Thakur, S., Schubart, J. R., & Carr, M. M. (2018). Parental perception of the perioperative experience for children with autism. *AORN Journal*, *108*(1), 34–43. https://doi.org/10.1002/aorn.12274

Berg, K. L., Acharya, K., Shiu, C.-S., & Msall, M. E. (2018). Delayed Diagnosis and Treatment Among Children with Autism Who Experience Adversity. *Journal of Autism and Developmental Disorders*, *48*(1), 45–54. https://doi.org/10.1007/s10803-017-3294-y

Besson, J. (1999). The neurobiology of pain. *The Lancet*, *353*(9164), 1610–1615. https://doi.org/10.1016/S0140-6736(99)01313-6

Bhat, A. N. (2020). Is Motor Impairment in Autism Spectrum Disorder Distinct from

Developmental Coordination Disorder A Report from the SPARK Study. *Physical Therapy*, *100*(4), 633–644. https://doi.org/10.1093/ptj/pzz190

Bhushan, B. (2015). Study of Facial Micro-expressions in Psychology. In M. K. Mandal & A. Awasthi (Eds.), *Understanding Facial Expressions in Communication: Cross-cultural and Multidisciplinary Perspectives* (pp. 265–286). Springer India. https://doi.org/10.1007/978-81-322-1934-7_13

Bird, G., Silani, G., Brindley, R., White, S., Frith, U., & Singer, T. (2010). Empathic brain responses in insula are modulated by levels of alexithymia but not autism. *Brain*, *133*(5), 1515–1525. https://doi.org/10.1093/brain/awq060

Bishop-Fitzpatrick, L., Mazefsky, C. A., Eack, S. M., & Minshew, N. J. (2017). Correlates of social functioning in autism spectrum disorder: The role of social cognition. *Research in Autism Spectrum Disorders*, *35*, 25–34. https://doi.org/10.1016/j.rasd.2016.11.013

Bitsika, V., & Sharpley, C. F. (2015). Differences in the Prevalence, Severity and Symptom Profiles of Depression in Boys and Adolescents with an Autism Spectrum Disorder versus Normally Developing Controls. *International Journal of Disability, Development and Education*, *62*(2), 158–167. https://doi.org/10.1080/1034912X.2014.998179

Blakemore, S. J., Tavassoli, T., Calò, S., Thomas, R. M., Catmur, C., Frith, U., & Haggard, P. (2006). Tactile sensitivity in Asperger syndrome. *Brain and Cognition*, *61*(1), 5–13. https://doi.org/10.1016/j.bandc.2005.12.013

Boston, A., & Sharpe, L. (2005). The role of threat-expectancy in acute pain: effects on attentional bias, coping strategy effectiveness and response to pain. *Pain*, *119*(1–3). https://journals.lww.com/pain/Fulltext/2005/12000/The_role_of_threat_expectancy_in_acute_pain_.19.aspx

Botvinick, M., & Braver, T. (2015). Motivation and Cognitive Control: From Behavior to Neural Mechanism. *Annual Review of Psychology*, *66*(1), 83–113. https://doi.org/10.1146/annurev-psych-010814-015044

Boudreaux, M. J., & Ozer, D. J. (2013). Goal conflict, goal striving, and psychological well-being. *Motivation and Emotion*, *37*(3), 433–443. https://doi.org/10.1007/s11031-012-9333-2

Bozzi, Y., Provenzano, G., & Casarosa, S. (2018). Neurobiological bases of autism–epilepsy comorbidity: a focus on excitation/inhibition imbalance. *European Journal of Neuroscience*, *47*(6), 534–548. https://doi.org/10.1111/ejn.13595

Breau, L. M., Camfield, C. S., McGrath, P. J., & Finley, G. A. (2007). Pain's impact on adaptive functioning. *Journal of Intellectual Disability Research*, *51*(2), 125–134. https://doi.org/10.1111/j.1365-2788.2006.00851.x

Breau, Lynn M., Camfield, C. S., Symons, F. J., Bodfish, J. W., MacKay, A., Allen Finley, G., & McGrath, P. J. (2003). Relation between pain and self-injurious behavior in nonverbal children with severe cognitive impairments. *Journal of Pediatrics*, *142*(5), 498–503. https://doi.org/10.1067/mpd.2003.163

Breau, Lynn M., McGrath, P. J., Craig, K. D., Santor, D., Cassidy, K. L., & Reid, G. J. (2001). Facial expression of children receiving immunizations: A principal components analysis of the child facial coding system. *Clinical Journal of Pain*, *17*(2), 178–186. https://doi.org/10.1097/00002508-200106000-00011

Breau, Lynn M, McGrath, P. J., Camfield, C. S., & Finley, A. G. (2002). Psychometric properties of the non-communicating children's pain checklist-revised. *Pain*, *99*(1). https://journals.lww.com/pain/Fulltext/2002/09000/Psychometric_properties_of_the_no

n_communicating.37.aspx

Bremer, E., & Cairney, J. (2018). The Interrelationship Between Motor Coordination and Adaptive Behavior in Children With Autism Spectrum Disorder. *Frontiers in Psychology*, *0*(NOV), 2350. https://doi.org/10.3389/FPSYG.2018.02350

Brewer, C., Brewer, C. L., & Baccei, M. L. (2020). The development of pain circuits and unique effects of neonatal injury. *Journal of Neural Transmission*, *127*(4), 467-479. https://doi.org/10.1007/s00702-019-02059-z

Broome, M. E., Bates, T. A., Lillis, P. P., & McGahee, T. . (1990). Children's medical fears, coping behaviors, and pain perceptions during a lumbar puncture. *Oncology Nursing Forum*, *17*(3), 361–367. https://europepmc.org/article/med/2342970

Brown, J. L., Sheffield, D., Leary, M. R., & Robinson, M. E. (2003). Social Support and Experimental Pain. *Psychosomatic Medicine*, *65*(2), 276–283. https://doi.org/10.1097/01.PSY.0000030388.62434.46

Bruce, V., Green, P., & Georgeson, M. (2003). *Visual perception: Physiology, psychology, & ecology* (4th Editio). Taylor & Francis.

Buckelew, S. P., Conway, R. ., Shutty, M. S., Lawrence, J. A., Grafing, M. R., Anderson, S. K., Hewett, J. E., & Keefe, F. J. (1992). Spontaneous coping strategies to manage acute pain and anxiety during electrodiagnostic studies. *Archives of Physical Medicine and Rehabilitation*, *73*(6), 594–598. https://pubmed.ncbi.nlm.nih.gov/1622311/

Buescher, K. L., Johnston, J. A., Parker, J. C., Smarr, K. L., Buckelew, S. P., Anderson, S. K., & Walker, S. E. (1991). Relationship of self-efficacy to pain behavior. *The Journal of Rheumatology*, *18*(7), 968–972. https://europepmc.org/article/med/1920330

Buonocore, M., Demartini, L., Aloisi, A. M., & Bonezzi, C. (2016). Dynamic Mechanical Allodynia-One Clinical Sign, Several Mechanisms: Five Illustrative Cases. *Pain Practice*, *16*(3), E48–E55. https://doi.org/10.1111/papr.12416

Burke, D., Mackenzie, R. A., Skuse, N. F., & Lethlean, A. K. (1975). Cutaneous afferent activity in median and radial nerve fascicles: A microelectrode study. *Journal of Neurology, Neurosurgery and Psychiatry*, *38*(9), 855–864. https://doi.org/10.1136/jnnp.38.9.855

Burns, J. W., Mullen, J. T., Higdon, L. J., Wei, J. M., & Lansky, D. (2000). Validity of the Pain Anxiety Symptoms Scale (PASS): Prediction of physical capacity variables. *Pain*, *84*(2–3), 247–252. https://doi.org/10.1016/S0304-3959(99)00218-3

Bursch, B., Ingman, K., Vitti, L., Hyman, P., & Zeltzer, L. K. (2004). Chronic pain in individuals with previously undiagnosed autistic spectrum disorders. *The Journal of Pain*, *5*(5), 290–295. https://doi.org/10.1016/J.JPAIN.2004.04.004

Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, *14*, 365. https://doi.org/10.1038/nrn3475

Cabanac, M. (1986). Money versus pain: experimental study of a conflict in humans. *Journal of the Experimental Analysis of Behavior*, *46*(1), 37–44. https://doi.org/10.1901/jeab.1986.46-37

Cain, D. M., Khasabov, S. G., & Simone, D. A. (2001). Response properties of mechanoreceptors and nociceptors in mouse glabrous skin: an in vivo study. *Journal of Neurophysiology*, *85*(4), 1561–1574. https://doi.org/10.1152/JN.2001.85.4.1561

5045 Camfield, C., & Camfield, P. (2015). Injuries from seizures are a serious, persistent problem
5046 in childhood onset epilepsy: A population-based study. *Seizure - European Journal of*
5047 *Epilepsy*, *27*, 80–83. https://doi.org/10.1016/j.seizure.2015.02.031

5048 Campbell, J. N., & Meyer, R. A. (2006). Mechanisms of Neuropathic Pain. *Neuron*, *52*(1),
5049 77–92. https://doi.org/10.1016/J.NEURON.2006.09.021

5050 Campbell J Lahuerta rcdo Med cir, J. A. (1983). Physical methods used in pain
5051 measurements: a review1. In *Journal of the Royal Society of Medicine* (Vol. 76).

5052 Cano, A., Gillis, M., Heinz, W., Geisser, M., & Foran, H. (2004). Marital functioning,
5053 chronic pain, and psychological distress. *Pain*, *107*(1–2), 99–106.
5054 https://doi.org/10.1016/j.pain.2003.10.003

5055 Carr, D. B., & Goudas, L. C. (1999). Acute pain. *The Lancet*, *353*(9169), 2051–2058.
5056 https://doi.org/10.1016/S0140-6736(99)03313-9

5057 Caruana, E. J., Roman, M., Hernández-Sánchez, J., & Solli, P. (2015). Longitudinal studies.
5058 *Journal of Thoracic Disease*, *7*(11), E537–E540. https://doi.org/10.3978/j.issn.2072-
5059 1439.2015.10.63

5060 Cascio, C. J., Foss-Feig, J. H., Heacock, J., Schauder, K. B., Loring, W. A., Rogers, B. P.,
5061 Pryweller, J. R., Newsom, C. R., Cockhren, J., Cao, A., & Bolton, S. (2014). Affective
5062 neural response to restricted interests in autism spectrum disorders. *Journal of Child*
5063 *Psychology and Psychiatry and Allied Disciplines*, *55*(2), 162–171.
5064 https://doi.org/10.1111/jcpp.12147

5065 Cascio, C. J., Moore, D., & McGlone, F. (2019). Social touch and human development.
5066 *Developmental Cognitive Neuroscience*, *35*, 5–11.

https://doi.org/10.1016/J.DCN.2018.04.009

Cascio, C., McGlone, F., Folger, S., Tannan, V., Baranek, G., Pelphrey, K. A., & Essick, G. (2008). Tactile perception in adults with autism: A multidimensional psychophysical study. *Journal of Autism and Developmental Disorders*, *38*(1), 127–137. https://doi.org/10.1007/s10803-007-0370-8

Cavanagh, P. R., & Komi, P. V. (1979). Electromechanical delay in human skeletal muscle under concentric and eccentric contractions. *European Journal of Applied Physiology and Occupational Physiology*, *42*(3), 159–163. https://doi.org/10.1007/BF00431022

Cesaroni, L., & Garber, M. (1991). Exploring the experience of autism through firsthand accounts. *Journal of Autism and Developmental Disorders*, *21*(3), 303–313. https://doi.org/10.1007/bf02207327

Chambers, C. T., Craig, K. D., & Bennett, S. M. (2002). The Impact of Maternal Behavior on Children's Pain Experiences: An Experimental Analysis. *Journal of Pediatric Psychology*, *27*(3), 293–301. https://doi.org/10.1093/JPEPSY/27.3.293

Chapman, C. R., Casey, K. L., Dubner, R., Foley, K. M., Gracely, R. H., & Reading, A. E. (1985). Pain measurement: an overview. *Pain*, *22*(1), 1–31. https://doi.org/10.1016/0304-3959(85)90145-9

Che, X., Cash, R., Ng, S. K., Fitzgerald, P., & Fitzgibbon, B. M. (2018). A Systematic Review of the Processes Underlying the Main and the Buffering Effect of Social Support on the Experience of Pain. *Clinical Journal of Pain*, *34*(11), 1061–1076. https://doi.org/10.1097/AJP.0000000000000624

Chen, Y.-H., Rodgers, J., & McConachie, H. (2009). Restricted and Repetitive Behaviours,

Sensory Processing and Cognitive Style in Children with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *39*(4), 635–642. https://doi.org/10.1007/s10803-008-0663-6

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. *Trends in Cognitive Sciences*, *16*(4), 231–239. https://doi.org/10.1016/J.TICS.2012.02.007

Cholemkery, H., Medda, J., Lempp, T., & Freitag, C. M. (2016). Classifying Autism Spectrum Disorders by ADI-R: Subtypes or Severity Gradient? *Journal of Autism and Developmental Disorders*, *46*(7), 2327–2339. https://doi.org/10.1007/s10803-016-2760-2

Chorney, J. M., McMurtry, C. M., Chambers, C. T., & Bakeman, R. (2015). Developing and modifying behavioral coding schemes in pediatric psychology: a practical guide. *Journal of Pediatric Psychology*, *40*(1), 154–164. https://doi.org/10.1093/jpepsy/jsu099

Chou, R., Fu, R., Carrino, J. A., & Deyo, R. A. (2009). Imaging strategies for low-back pain: systematic review and meta-analysis. *The Lancet*, *373*(9662), 463–472. https://doi.org/10.1016/S0140-6736(09)60172-0

Christley, R. M. (2010). Power and error: Increased risk of false positive results in underpowered studies. *Open Epidemiology Journal*, *3*, 16–19. https://doi.org/10.2174/1874297101003010016

Claes, N., Crombez, G., & Vlaeyen, J. W. S. (2015). Pain-avoidance versus reward-seeking: an experimental investigation. *Pain*, *156*(8). https://journals.lww.com/pain/Fulltext/2015/08000/Pain_avoidance_versus_reward_seeking__an.12.aspx

Claes, N., Karos, K., Meulders, A., Crombez, G., & Vlaeyen, J. W. S. (2014a). Competing Goals Attenuate Avoidance Behavior in the Context of Pain. *The Journal of Pain*, *15*(11), 1120–1129. https://doi.org/10.1016/j.jpain.2014.08.003

Claes, N., Karos, K., Meulders, A., Crombez, G., & Vlaeyen, J. W. S. (2014b). Competing Goals Attenuate Avoidance Behavior in the Context of Pain. *The Journal of Pain*, *15*(11), 1120–1129. https://doi.org/10.1016/J.JPAIN.2014.08.003

Claes, N., Vlaeyen, J. W. S., & Crombez, G. (2016a). Pain in context: Cues predicting a reward decrease fear of movement related pain and avoidance behavior. *Behaviour Research and Therapy*, *84*, 35–44. https://doi.org/10.1016/j.brat.2016.07.004

Claes, N., Vlaeyen, J. W. S., & Crombez, G. (2016b). Pain in context: Cues predicting a reward decrease fear of movement related pain and avoidance behavior. *Behaviour Research and Therapy*, *84*, 35–44. https://doi.org/10.1016/j.brat.2016.07.004

Clarke, C. (2015). Autism Spectrum Disorder and Amplified Pain. *Case Reports in Psychiatry*, *2015*, 1–4. https://doi.org/10.1155/2015/930874

Classification of Chronic Pain, Second Edition (Revised) | International Association for the Study of Pain (IASP). (n.d.). Retrieved September 27, 2021, from https://www.iasp-pain.org/publications/free-ebooks/classification-of-chronic-pain-second-edition-revised/

Cleeland, C. S., Nakamura, Y., Howland, E. W., Morgan, N. R., Edwards, K. R., & Backonja, M. (1996). Effects of oral morphine on cold presser tolerance time and neuropsychological performance. *Neuropsychopharmacology*, *15*(3), 252–262. https://doi.org/10.1016/0893-133X(95)00205-R

Cleeland, C. S., Nakamura, Y., Mendoza, T. R., Edwards, K. R., Douglas, J., & Serlin, R. C.

(1996). Dimensions of the impact of cancer pain in a four country sample: New information from multidimensional scaling. *Pain*, *67*(2–3), 267–273. https://doi.org/10.1016/0304-3959(96)03131-4

Cohen, I. L., & Flory, M. J. (2019). Autism Spectrum Disorder Decision Tree Subgroups Predict Adaptive Behavior and Autism Severity Trajectories in Children with ASD. *Journal of Autism and Developmental Disorders*, *49*(4), 1423–1437. https://doi.org/10.1007/s10803-018-3830-4

Colloca, L., & Benedetti, F. (2009). Placebo analgesia induced by social observational learning. *Pain*, *144*(1–2), 28–34. https://doi.org/10.1016/j.pain.2009.01.033

Corden, B., Chilvers, R., & Skuse, D. (2008). Avoidance of emotionally arousing stimuli predicts social-perceptual impairment in Asperger's syndrome. *Neuropsychologia*, *46*(1), 137–147. https://doi.org/10.1016/j.neuropsychologia.2007.08.005

Costa, A. S., Dogan, I., Schulz, J. B., & Reetz, K. (2019). Going beyond the mean: Intraindividual variability of cognitive performance in prodromal and early neurodegenerative disorders. *Clinical Neuropsychologist*, *33*(2), 369–389. https://doi.org/10.1080/13854046.2018.1533587

Craig, K. D. (2009). The social communication model of pain. *Canadian Psychology*, *50*(1), 22–32. https://doi.org/10.1037/a0014772

Craig, K. D. (2015). Social communication model of pain. *Pain*, *156*(7), 1198–1199. https://doi.org/10.1097/j.pain.0000000000000185

Craig, K. D., Hyde, S. A., & Patrick, C. J. (1991). Genuine, suppressed and faked facial behavior during exacerbation of chronic low back pain. *Pain*, *46*(2), 161–171.

https://doi.org/10.1016/0304-3959(91)90071-5

Craig, K. D., & Patrick, C. J. (1985). Facial Expression During Induced Pain. *Journal of Personality and Social Psychology*, *48*(4), 1080–1091. https://doi.org/10.1037/0022-3514.48.4.1089

Craig, K. D., Prkachin, K. M., & Grunau, R. E. (2001). The facial expression of pain. In *Handbook of pain assessment, 2nd ed.* (pp. 153–169). The Guilford Press.

Craig, K. D., & Weiss, S. M. (1971). Vicarious influences on pain-threshold determinations. *Journal of Personality and Social Psychology*, *19*(1), 53–59. https://doi.org/10.1037/h0031097

Craig, K. D., Whitfield, M. F., Grunau, R. V. E., Linton, J., & Hadjistavropoulos, H. D. (1993). Pain in the preterm neonate: behavioural and physiological indices. *Pain*, *52*(3), 287–299. https://doi.org/10.1016/0304-3959(93)90162-I

Craik, F. I. M., & Bialystok, E. (2006). Cognition through the lifespan: Mechanisms of change. *Trends in Cognitive Sciences*, *10*(3), 131–138. https://doi.org/10.1016/j.tics.2006.01.007

Crombez, G., Baeyens, F., & Eelen, P. (1994). Sensory and temporal information about impending pain: The influence of predictability on pain. *Behaviour Research and Therapy*, *32*(6), 611–622. https://doi.org/10.1016/0005-7967(94)90015-9

Crombez, Geert, Eccleston, C., Damme, S. Van, Vlaeyen, J. W. S., & Karoly, P. (2012). *Fear-Avoidance Model of Chronic Pain*. *28*(6), 475–483. https://doi.org/10.1097/AJP.0b013e3182385392

Crombez, Geert, Eccleston, C., Van Damme, S., Vlaeyen, J. W. S., & Karoly, P. (2012).

5178 Fear-Avoidance Model of Chronic Pain: The Next Generation. *The Clinical Journal of*
5179 *Pain*, *28*(6). https://doi.org/10.1097/AJP.0b013e3182385392.

5180 Crombez, Geert, Van Damme, S., & Eccleston, C. (2005). Hypervigilance to pain: An
5181 experimental and clinical analysis. *Pain*, *116*(1), 4–7.
5182 https://doi.org/10.1016/j.pain.2005.03.035

5183 Cronbach, L. J. (1957). The two disciplines of scientific psychology. *American Psychologist*,
5184 *12*(11), 671–684. https://doi.org/10.1037/h0043943

5185 D'Amico, E. J., Neilands, T. B., & Zambarano, R. (2001). Power analysis for multivariate
5186 and repeated measures designs: a flexible approach using the SPSS MANOVA
5187 procedure. *Behavior Research Methods, Instruments, & Computers : A Journal of the*
5188 *Psychonomic Society, Inc*, *33*(4), 479–484. https://doi.org/10.3758/BF03195405

5189 Dalton, K. M., Nacewicz, B. M., Johnstone, T., Schaefer, H. S., Gernsbacher, M. A.,
5190 Goldsmith, H. H., Alexander, A. L., & Davidson, R. J. (2005). Gaze fixation and the
5191 neural circuitry of face processing in autism. *Nature Neuroscience*, *8*(4), 519–526.
5192 https://doi.org/10.1038/nn1421

5193 Davidson, M. M., & Ellis Weismer, S. (2017). A Discrepancy in Comprehension and
5194 Production in Early Language Development in ASD: Is it Clinically Relevant? *Journal*
5195 *of Autism and Developmental Disorders*, *47*(7), 2163–2175.
5196 https://doi.org/10.1007/s10803-017-3135-z

5197 de Faria, C. A., Alves, H. V. D., & Charchat-Fichman, H. (2015). The most frequently used
5198 tests for assessing executive functions in aging. *Dementia e Neuropsychologia*, *9*(2),
5199 149–155. https://doi.org/10.1590/1980-57642015dn92000009

5200 Delehanty, A. D., Stronach, S., Guthrie, W., Slate, E., & Wetherby, A. M. (2018). Verbal and
5201 nonverbal outcomes of toddlers with and without autism spectrum disorder, language
5202 delay, and global developmental delay. *Autism & Developmental Language*
5203 *Impairments*, *3*, 239694151876476. https://doi.org/10.1177/2396941518764764

5204 Deliens, G., Leproult, R., Schmitz, R., Destrebecqz, A., & Peigneux, P. (2015). Sleep
5205 Disturbances in Autism Spectrum Disorders. *Review Journal of Autism and*
5206 *Developmental Disorders*, *2*(4), 343–356. https://doi.org/10.1007/s40489-015-0057-6

5207 Dell'osso, L., & Pini, S. (2012). What Did We Learn from Research on Comorbidity In
5208 Psychiatry? Advantages and Limitations in the Forthcoming DSM-V Era. *Clinical*
5209 *Practice and Epidemiology in Mental Health*, *8*, 180–184.
5210 https://doi.org/10.2174/1745017901208010180

5211 Delmas, P., Hao, J., & Rodat-Despoix, L. (2011). Molecular mechanisms of
5212 mechanotransduction in mammalian sensory neurons. *Nature Reviews Neuroscience*,
5213 *12*(3), 139–153. https://doi.org/10.1038/nrn2993

5214 Delmonte, S., Balsters, J. H., McGrath, J., Fitzgerald, J., Brennan, S., Fagan, A. J., &
5215 Gallagher, L. (2012). Social and monetary reward processing in autism spectrum
5216 disorders. *Molecular Autism*, *3*(1), 7. https://doi.org/10.1186/2040-2392-3-7

5217 Demetriou, E. A., Lampit, A., Quintana, D. S., Naismith, S. L., Song, Y. J. C., Pye, J. E.,
5218 Hickie, I., & Guastella, A. J. (2018). Autism spectrum disorders: A meta-analysis of
5219 executive function. *Molecular Psychiatry*, *23*(5), 1198–1204.
5220 https://doi.org/10.1038/mp.2017.75

5221 DeWall, C. N., & Baumeister, R. F. (2006). Alone but feeling no pain: Effects of social
5222 exclusion on physical pain tolerance and pain threshold, affective forecasting, and

interpersonal empathy. *Journal of Personality and Social Psychology*, *91*(1), 1–15. https://doi.org/10.1037/0022-3514.91.1.1

Djouhri, L., & Lawson, S. N. (2004). Aβ-fiber nociceptive primary afferent neurons: a review of incidence and properties in relation to other afferent A-fiber neurons in mammals. *Brain Research Reviews*, *46*(2), 131–145. https://doi.org/10.1016/J.BRAINRESREV.2004.07.015

Domjan, M. (2017). The essentials of conditioning and learning (4th ed.). In *The essentials of conditioning and learning (4th ed.).* American Psychological Association. https://doi.org/10.1037/0000057-000

Donate, G., Bartlett, M. S., Hager, J. C., Ekman, P., & Sejnowski, T. J. (1999). Classifying facial actions. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, *21*(10), 974–989. https://doi.org/10.1109/34.799905

Dorner, T. E., Muckenhuber, J., Stronegger, W. J., Rsky, É., Gustorff, B., & Freidl, W. (2011). The impact of socio-economic status on pain and the perception of disability due to pain. *European Journal of Pain*, *15*(1), 103–109. https://doi.org/10.1016/j.ejpain.2010.05.013

Doshi-Velez, F., Ge, Y., & Kohane, I. (2014). Comorbidity clusters in autism spectrum disorders: an electronic health record time-series analysis. *Pediatrics*, *133*(1), e54–e63. https://doi.org/10.1542/peds.2013-0819

Downie, W. W., Leatham, P. A., Rhind, V. M., Wright, V., Branco, J. A., & Anderson, J. A. (1978). Studies with pain rating scales. *Annals of the Rheumatic Diseases*, *37*(4), 378–381. https://doi.org/10.1136/ard.37.4.378

5245 Dubin, A. E., & Patapoutian, A. (2010). Nociceptors: the sensors of the pain pathway. *The*
5246 *Journal of Clinical Investigation*, *120*(11), 3760–3772. https://doi.org/10.1172/JCI42843

5247 Dubois, A., Boudjarane, M., Le Fur-Bonnabesse, A., Dion, A., L'heveder, G., Quinio, B.,
5248 Walter, M., Marchand, S., & Bodéré, C. (2020). Pain Modulation Mechanisms in ASD
5249 Adults. *Journal of Autism and Developmental Disorders*, *50*(8), 2931–2940.
5250 https://doi.org/10.1007/s10803-019-04361-x

5251 Duerden, E. G., Card, D., Roberts, S. W., Mak-Fan, K. M., Chakravarty, M. M., Lerch, J. P.,
5252 & Taylor, M. J. (2014). Self-injurious behaviours are associated with alterations in the
5253 somatosensory system in children with autism spectrum disorder. *Brain Structure and*
5254 *Function*, *219*(4), 1251–1261. https://doi.org/10.1007/s00429-013-0562-2

5255 Duerden, E. G., Taylor, M. J., Lee, M., McGrath, P. A., Davis, K. D., & Roberts, S. W.
5256 (2015). Decreased sensitivity to thermal stimuli in adolescents with autism spectrum
5257 disorder: Relation to symptomatology and cognitive ability. *Journal of Pain*, *16*(5), 463–
5258 471. https://doi.org/10.1016/j.jpain.2015.02.001

5259 Dunn, W., Saiter, J., & Rinner, L. (2002). Asperger Syndrome and Sensory Processing: A
5260 Conceptual Model and Guidance for Intervention Planning. *Focus on Autism and Other*
5261 *Developmental Disabilities*, *17*(3), 172–185.
5262 https://doi.org/10.1177/10883576020170030701

5263 Dunsmoor, J. E., & Paz, R. (2015). Fear Generalization and Anxiety: Behavioral and Neural
5264 Mechanisms. *Biological Psychiatry*, *78*(5), 336–343.
5265 https://doi.org/10.1016/J.BIOPSYCH.2015.04.010

5266 Eccleston, C. (2013). A normal psychology of everyday pain. *International Journal of*
5267 *Clinical Practice*, *67*(SUPPL. 178), 47–50. https://doi.org/10.1111/ijcp.12051

5268 Eccleston, Chris, & Crombez, G. (1999). Pain demands attention: A cognitive-affective
5269 model of the interruptive function of pain. *Psychological Bulletin*, *125*(3), 356–366.
5270 https://doi.org/10.1037/0033-2909.125.3.356

5271 Edens, J. L., & Gil, K. M. (1995). Experimental induction of pain: Utility in the study of
5272 clinical pain. *Behavior Therapy*, *26*(2), 197–216. https://doi.org/10.1016/S0005-
5273 7894(05)80102-9

5274 Edwards, R., Eccleston, C., & Keogh, E. (2017). Observer influences on pain: An
5275 experimental series examining same-sex and opposite-sex friends, strangers, and
5276 romantic partners. *Pain*, *158*(5), 846–855.
5277 https://doi.org/10.1097/j.pain.0000000000000840

5278 Eisenberger, N. I., Master, S. L., Inagaki, T. K., Taylor, S. E., Shirinyan, D., Lieberman, M.
5279 D., & Naliboff, B. D. (2011). Attachment figures activate a safety signal-related neural
5280 region and reduce pain experience. *Proceedings of the National Academy of Sciences of*
5281 *the United States of America*, *108*(28), 11721–11726.
5282 https://doi.org/10.1073/pnas.1108239108

5283 Ekman, P. (1992). Facial Expressions of Emotion: New Findings, New Questions.
5284 *Psychological Science*, *3*(1), 34–38. https://doi.org/10.1111/j.1467-9280.1992.tb00253.x

5285 Elstein, A. S., & Schwartz, A. (2002). Clinical problem solving and diagnostic decision
5286 making: selective review of the cognitive literature. *British Medical Journal*, *324*(7339),
5287 729–732. https://doi.org/10.1136/bmj.324.7339.729

5288 Elwin, M., Ek, L., Kjellin, L., & Schröder, A. (2013). Too much or too little: Hyper- and
5289 hypo-reactivity in high-functioning autism spectrum conditions. *Journal of Intellectual*
5290 *and Developmental Disability*, *38*(3), 232–241.

https://doi.org/10.3109/13668250.2013.815694

Elwin, M., Ek, L., Schröder, A., & Kjellin, L. (2012). Autobiographical Accounts of Sensing in Asperger Syndrome and High-Functioning Autism. *Archives of Psychiatric Nursing*, *26*(5), 420–429. https://doi.org/10.1016/j.apnu.2011.10.003

Enna, S. J., & McCarson, K. E. (2006). The Role of GABA in the Mediation and Perception of Pain. *Advances in Pharmacology*, *54*, 1–27. https://doi.org/10.1016/S1054-3589(06)54001-3

Failla, M. D., Gerdes, M. B., Williams, Z. J., Moore, D. J., & Cascio, C. J. (2020). Increased pain sensitivity and pain-related anxiety in individuals with autism. *Pain Reports*, *5*(6), e861. https://doi.org/10.1097/pr9.0000000000000861

Failla, M. D., Moana-Filho, E. J., Essick, G. K., Baranek, G. T., Rogers, B. P., & Cascio, C. J. (2018a). Initially intact neural responses to pain in autism are diminished during sustained pain. *Autism*, *22*(6), 669–683. https://doi.org/10.1177/1362361317696043

Failla, M. D., Moana-Filho, E. J., Essick, G. K., Baranek, G. T., Rogers, B. P., & Cascio, C. J. (2018b). Initially intact neural responses to pain in autism are diminished during sustained pain. *Autism*, *22*(6), 669–683. https://doi.org/10.1177/1362361317696043

Fan, Y. T., Chen, C., Chen, S. C., Decety, J., & Cheng, Y. (2014). Empathic arousal and social understanding in individuals with autism: Evidence from fMRI and ERP measurements. *Social Cognitive and Affective Neuroscience*, *9*(8), 1203–1213. https://doi.org/10.1093/scan/nst101

Faso, D. J., Sasson, N. J., & Pinkham, A. E. (2015). Evaluating Posed and Evoked Facial Expressions of Emotion from Adults with Autism Spectrum Disorder. *Journal of Autism*

5313 *and Developmental Disorders*, *45*(1), 75–89. https://doi.org/10.1007/s10803-014-2194-7

5314 Ferraz, M. B., Quaresma, M. R., Aquino, L. R. L., Atra, E., Tugwell, P., & Goldsmith, C. H.
5315 (1990). Reliability of pain scales in the assessment of literate and illiterate patients with
5316 rheumatoid arthritis. *Journal of Rheumatology*, *17*(8), 1022–1024.

5317 Ferris, L. J., Jetten, J., Molenberghs, P., Bastian, B., & Karnadewi, F. (2016). Increased Pain
5318 Communication following Multiple Group Memberships Salience Leads to a Relative
5319 Reduction in Pain-Related Brain Activity. *PLOS ONE*, *11*(9), e0163117.
5320 https://doi.org/10.1371/JOURNAL.PONE.0163117

5321 Fields, H. (2004). State-dependent opioid control of pain. *Nature Reviews Neuroscience*,
5322 *5*(7), 565–575. https://doi.org/10.1038/nrn1431

5323 Fields, H. L. (1999). Pain: An unpleasant topic. *Pain*, *82*(SUPPL.1).
5324 https://doi.org/10.1016/S0304-3959(99)00139-6

5325 Finan, P. H., Goodin, B. R., & Smith, M. T. (2013). The association of sleep and pain: an
5326 update and a path forward. *The Journal of Pain : Official Journal of the American Pain*
5327 *Society*, *14*(12), 1539–1552. https://doi.org/10.1016/j.jpain.2013.08.007

5328 Fishbain, D. (2002). Pain and Psychopathology. In V. S. B. T.-E. of the H. B. Ramachandran
5329 (Ed.), *Encyclopedia of the Human Brain* (pp. 763–775). Academic Press.
5330 https://doi.org/https://doi.org/10.1016/B0-12-227210-2/00265-X

5331 Fitzgerald, M. (1991). Development of pain mechanisms. *British Medical Bulletin*, *47*(3),
5332 667–675. https://doi.org/10.1093/oxfordjournals.bmb.a072499

5333 Flectcher-Watson, S., & Happe, F. (2019). *Autism A New Introduction to Psychological*
5334 *Theory and CUrrent Debate* (2nd ed.). Routledge.

Flensborg-Madsen, T., & Mortensen, E. L. (2018). Associations of Early Developmental Milestones With Adult Intelligence. *Child Development*, *89*(2), 638–648. https://doi.org/10.1111/cdev.12760

Foss-Feig, J. H., Heacock, J. L., & Cascio, C. J. (2012). Tactile responsiveness patterns and their association with core features in autism spectrum disorders. *Research in Autism Spectrum Disorders*, *6*(1), 337–344. https://doi.org/10.1016/j.rasd.2011.06.007

Fountain, C., King, M. D., & Bearman, P. S. (2011). Age of diagnosis for autism: individual and community factors across 10 birth cohorts. *Journal of Epidemiology & Community Health*, *65*(6), 503–510. https://doi.org/10.1136/jech.2009.104588

Frith, U., & Happe, F. (1994). Autism: beyond "theory of mind"; *Cognition*, *50*(1-3), 115–132. https://doi.org/ 10.1016/0010-0277(94)90024-8.

Fründt, O., Grashorn, W., Schöttle, D., Peiker, I., David, N., Engel, A. K., Forkmann, K., Wrobel, N., Münchau, A., & Bingel, U. (2017). Quantitative Sensory Testing in adults with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *47*(4), 1183–1192. https://doi.org/10.1007/s10803-017-3041-4

Gandhi, W., Becker, S., & Schweinhardt, P. (2013). Pain increases motivational drive to obtain reward, but does not affect associated hedonic responses: A behavioural study in healthy volunteers. *European Journal of Pain*, *17*(7), 1093–1103. https://doi.org/10.1002/j.1532-2149.2012.00281.x

Garcia-Villamisar, D., Moore, D., & Garcia-Martínez, M. (2019a). Internalizing Symptoms Mediate the Relation Between Acute Pain and Autism in Adults. *Journal of Autism and Developmental Disorders*, *49*(1), 270–278. https://doi.org/10.1007/s10803-018-3765-9

Garcia-Villamisar, D., Moore, D., & Garcia-Martínez, M. (2019b). Internalizing Symptoms Mediate the Relation Between Acute Pain and Autism in Adults. *Journal of Autism and Developmental Disorders*, *49*(1), 270–278. https://doi.org/10.1007/s10803-018-3765-9

Garin, O. (2014). Ceiling Effect. In *Encyclopedia of Quality of Life and Well-Being Research* (pp. 631–633). Springer Netherlands. https://doi.org/10.1007/978-94-007-0753-5_296

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The Biopsychosocial Approach to Chronic Pain: Scientific Advances and Future Directions. *Psychological Bulletin*, *133*(4), 581–624. https://doi.org/10.1037/0033-2909.133.4.581

George, S. Z., Dannecker, E. A., & Robinson, M. E. (2006). Fear of pain, not pain catastrophizing, predicts acute pain intensity, but neither factor predicts tolerance or blood pressure reactivity: An experimental investigation in pain-free individuals. *European Journal of Pain*, *10*(5), 457. https://doi.org/10.1016/j.ejpain.2005.06.007

Georgiades, S., Bishop, S. L., & Frazier, T. (2017). Editorial Perspective: Longitudinal research in autism - introducing the concept of 'chronogeneity.' *Journal of Child Psychology and Psychiatry*, *58*(5), 634–636. https://doi.org/10.1111/jcpp.12690

Geurts, H. M., Grasman, R. P. P. P., Verté, S., Oosterlaan, J., Roeyers, H., van Kammen, S. M., & Sergeant, J. A. (2008). Intra-individual variability in ADHD, autism spectrum disorders and Tourette's syndrome. *Neuropsychologia*, *46*(13), 3030–3041. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2008.06.013

Gierthmühlen, J., Maier, C., Baron, R., Tölle, T., Treede, R.-D., Birbaumer, N., Huge, V., Koroschetz, J., Krumova, E. K., Lauchart, M., Maihöfner, C., Richter, H., & Westermann, A. (2012). Sensory signs in complex regional pain syndrome and peripheral nerve injury. *Pain*, *153*(4), 765–774.

https://doi.org/10.1016/j.pain.2011.11.009

Gilbert-MacLeod, C. A., Craig, K. D., Rocha, E. M., & Mathias, M. D. (2000). Everyday Pain Responses in Children With and Without Developmental Delays. *Journal of Pediatric Psychology*, *25*(5), 301–308. https://doi.org/10.1093/jpepsy/25.5.301

Gillberg, C., & Coleman, M. (2000). *The biology of the autistic syndromes*. Mac Keith Press. https://books.google.co.uk/books?hl=en&lr=&id=VZHruMg-c_EC&oi=fnd&pg=PR7&dq=the+biology+of+the+autistic+syndromes&ots=GsEb5dJyV3&sig=hCSOMW1kFhi1OND522hpS9L4I44#v=onepage&q=the biology of the autistic syndromes&f=false

Gliga, T., Jones, E. J. H., Bedford, R., Charman, T., & Johnson, M. H. (2014). From early markers to neuro-developmental mechanisms of autism. *Developmental Review*, *34*(3), 189–207. https://doi.org/10.1016/J.DR.2014.05.003

Glogan, E., Gatzounis, R., Vandael, K., Franssen, M., Vlaeyen, J. W. S., & Meulders, A. (2020). Investigating pain-related avoidance behavior using a robotic arm-reaching paradigm. *Journal of Visualized Experiments*, *2020*(164), 1–26. https://doi.org/10.3791/61717

Goesling, J., Clauw, D. J., & Hassett, A. L. (2013). Pain and Depression: An Integrative Review of Neurobiological and Psychological Factors. *Current Psychiatry Reports*, *15*(12), 421. https://doi.org/10.1007/s11920-013-0421-0

Goldstein, P., Shamay-Tsoory, S. G., Yellinek, S., & Weissman-Fogel, I. (2016). Empathy Predicts an Experimental Pain Reduction During Touch. *Journal of Pain*, *17*(10), 1049–1057. https://doi.org/10.1016/j.jpain.2016.06.007

5402 Goodman, J. E., & McGrath, P. J. (2003). Mothers' modeling influences children's pain
5403 during a cold pressor task. *Pain*, *104*(3), 559–565. https://doi.org/10.1016/S0304-
5404 3959(03)00090-3

5405 Gordon, I., Voos, A. C., Bennett, R. H., Bolling, D. Z., Pelphrey, K. A., & Kaiser, M. D.
5406 (2013). Brain mechanisms for processing affective touch. *Human Brain Mapping*, *34*(4),
5407 914–922. https://doi.org/10.1002/hbm.21480

5408 Goubert, L., Vervoort, T., & Crombez, G. (2009). Pain demands attention from others: The
5409 approach/avoidance paradox. *Pain*, *143*(1–2), 5–6.
5410 https://doi.org/10.1016/j.pain.2009.02.023

5411 Goubert, L., Vlaeyen, J. W. S., Crombez, G., & Craig, K. D. (2011). Learning about pain
5412 from others: An observational learning account. *Journal of Pain*, *12*(2), 167–174.
5413 https://doi.org/10.1016/j.jpain.2010.10.001

5414 Goulet, M.-A., & Cousineau, D. (2019). The Power of Replicated Measures to Increase
5415 Statistical Power, *2*(3), 199–213. https://doi.org/10.1177/2515245919849434

5416 Gracely, R. H. (2013). Studies of Pain in Human Subjects. In S. B. McMahon, M.
5417 Koltzenburg, I. Tracey, & D. C. Turk (Eds.), *Wall and Melzack's Textbook of Pain* (6th
5418 ed., pp. 283–300). Elsevier.

5419 Grandin, T. (1992). An Inside View of Autism. In *High-Functioning Individuals with Autism*
5420 (pp. 105–126). Springer US. https://doi.org/10.1007/978-1-4899-2456-8_6

5421 Grandin, T. (1995). *Thinking in pictures : and other reports from my life with autism*.
5422 Doubleday.
5423 https://books.google.co.uk/books/about/Thinking_in_Pictures.html?id=15J0M8uO5PgC

5424 &redir_esc=y

5425 Granovsky, Y., Matre, D., Sokolik, A., Lorenz, J., & Casey, K. L. (2005). Thermoreceptive
5426 innervation of human glabrous and hairy skin: A contact heat evoked potential analysis.
5427 *Pain*, *115*(3), 238–247. https://doi.org/10.1016/j.pain.2005.02.017

5428 Green, D., Chandler, S., Charman, T., Simonoff, E., & Baird, G. (2016). Brief Report: DSM-
5429 5 Sensory Behaviours in Children With and Without an Autism Spectrum Disorder.
5430 *Journal of Autism and Developmental Disorders*, *46*(11), 3597–3606.
5431 https://doi.org/10.1007/s10803-016-2881-7

5432 Gröne, E., Crispin, A., Fleckenstein, J., Irnich, D., Treede, R. D., & Lang, P. M. (2012). Test
5433 order of quantitative sensory testing facilitates mechanical hyperalgesia in healthy
5434 volunteers. *Journal of Pain*, *13*(1), 73–80. https://doi.org/10.1016/j.jpain.2011.10.005

5435 Gross, T. F. (2004). The perception of four basic emotions in human and nonhuman faces by
5436 children with autism and other developmental disabilities. *Journal of Abnormal Child*
5437 *Psychology*, *32*(5), 469–480. https://doi.org/10.1023/B:JACP.0000037777.17698.01

5438 Gross, T. F. (2008). Recognition of immaturity and emotional expressions in blended faces
5439 by children with autism and other developmental disabilities. *Journal of Autism and*
5440 *Developmental Disorders*, *38*(2), 297–311. https://doi.org/10.1007/s10803-007-0391-3

5441 Güçlü, B., Tanidir, C., Mukaddes, N. M., & Ünal, F. (2007). Tactile sensitivity of normal and
5442 autistic children. *Somatosensory and Motor Research*, *24*(1–2), 21–33.
5443 https://doi.org/10.1080/08990220601179418

5444 Gulsrud, A. C., Kasari, C., Freeman, S., & Paparella, T. (2007). Children with autism's
5445 response to novel stimuli while participating in interventions targeting joint attention or

symbolic play skills. *Autism*, *11*(6), 535–546. https://doi.org/10.1177/1362361307083255

Guo, Y., Logan, H. L., Glueck, D. H., & Muller, K. E. (2013). Selecting a sample size for studies with repeated measures. *BMC Medical Research Methodology*, *13*(1), 1–8. https://doi.org/10.1186/1471-2288-13-100

Hadjistavropoulos, T., Craig, K. D., Duck, S., Cano, A., Goubert, L., Jackson, P. L., Mogil, J. S., Rainville, P., Sullivan, M. J. L., Amanda, A. C., Vervoort, T., & Fitzgerald, T. D. (2011). A Biopsychosocial Formulation of Pain Communication. *Psychological Bulletin*, *137*(6), 910–939. https://doi.org/10.1037/a0023876

Hadjistavropoulos, T., Craig, K. D., Duck, S., Cano, A., Goubert, L., Jackson, P. L., Mogil, J. S., Rainville, P., Sullivan, M. J. L., Williams, A. C. de C., Vervoort, T., & Fitzgerald, T. D. (2011). A biopsychosocial formulation of pain communication. *Psychological Bulletin*, *137*(6), 910–939. https://doi.org/10.1037/a0023876

Hadjistavropoulos, T., Craig, K. D., & Fuchs-Lacelle, S. (2004). Social Influences and the Communication of Pain. In T. Hadjistavropoulos & K. D. Craig (Eds.), *Pain: Psychological perspectives*, 87–112. Lawrence Erlbaum Associates Publishers.

Handen, B. L., Mazefsky, C. A., Gabriels, R. L., Pedersen, K. A., Wallace, M., Siegel, M., Erickson, C., Gabriels, R. L., Kaplan, D., Morrow, E. M., Righi, G., Santangelo, S. L., Wink, L., Benevides, J., Beresford, C., Best, C., Bowen, K., Dechant, B., Dixon, J., … Tager-Flusberg, H. (2018). Risk Factors for Self-injurious Behavior in an Inpatient Psychiatric Sample of Children with Autism Spectrum Disorder: A Naturalistic Observation Study. *Journal of Autism and Developmental Disorders*, *48*(11), 3678–3688. https://doi.org/10.1007/s10803-017-3460-2

Hansen, C., Hopf, H. C., & Treede, R. D. (1996). Paradoxical heat sensation in patients with multiple sclerosis. *Brain*, *119*(5), 1729–1736. https://doi.org/10.1093/brain/119.5.1729

Hansson, P., Backonja, M., & Bouhassira, D. (2007). Usefulness and limitations of quantitative sensory testing: Clinical and research application in neuropathic pain states. *Pain*, *129*(3), 256–259. https://doi.org/10.1016/j.pain.2007.03.030

Happé, F., & Frith, U. (1996). The neuropsychology of autism. *Brain*, *119*(4), 1377–1400. https://doi.org/10.1093/brain/119.4.1377

Harms, M. B., Martin, A., & Wallace, G. L. (2010). Facial emotion recognition in autism spectrum disorders: A review of behavioral and neuroimaging studies. In *Neuropsychology Review*, *20*(3), 290–322. https://doi.org/10.1007/s11065-010-9138-6

Hasenbring, M. I., & Verbunt, J. A. (2010). Fear-avoidance and Endurance-related Responses to Pain: New Models of Behavior and Their Consequences for Clinical Practice. *The Clinical Journal of Pain*, *26*(9), 747–753. https://doi.org/10.1097/AJP.0b013e3181e104f2

Hatfield, L. (2014). Neonatal pain: What′s age got to do with it? *Surgical Neurology International*, *5*(14), 479. https://doi.org/10.4103/2152-7806.144630

Head, H. (1893). On Disturbances of Sensation with Especial Reference to the Pain of Visceral Disease. *Brain*, *16*(1–2), 1–133. https://doi.org/10.1093/brain/16.1-2.1

Heinricher, M. M., Tavares, I., Leith, J. L., & Lumb, B. M. (2009). Descending control of nociception: Specificity, recruitment and plasticity. *Brain Research Reviews*, *60*(1), 214–225. https://doi.org/10.1016/J.BRAINRESREV.2008.12.009

Heliövaara, M., Mäkelä, M., Knekt, P., impivaara, O., & Aromaa, A. (1991). Determinants of

sciatica and low-back pain. *Spine*, *16*(6), 608–614. https://doi.org/10.1097/00007632-199106000-00002

Henshel, R. L. (1980). The purposes of laboratory experimentation and the virtues of deliberate artificiality. *Journal of Experimental Social Psychology*, *16*(5), 466–478. https://doi.org/https://doi.org/10.1016/0022-1031(80)90052-9

Hering, E., Epstein, R., Elroy, S., Iancu, D. R., & Zelnik, N. (1999). Sleep Patterns in Autistic Children. *Journal of Autism and Developmental Disorders*, *29*(2), 143–147. https://doi.org/10.1023/A:1023092627223

Herrero, J. F., Laird, J. M. A., & Lopez-Garcia, J. A. (2000). Wind-up of spinal cord neurones and pain sensation: Much ado about something? *Progress in Neurobiology*, *61*(2), 169–203. https://doi.org/10.1016/S0301-0082(99)00051-9

Hertz-Picciotto, I., & Delwiche, L. (2009). The Rise in Autism and the Role of Age at Diagnosis. *Epidemiology*, *20*(1), 84–90. https://doi.org/10.1097/EDE.0b013e3181902d15

Hird, E. J., Charalambous, C., El-Deredy, W., Jones, A. K., & Talmi, D. (2019). Boundary effects of expectation in human pain perception. *Scientific Reports*, *9*(1), 1–13. https://doi.org/10.1038/s41598-019-45811-x

Hirsh, A. T., George, S. Z., Bialosky, J. E., & Robinson, M. E. (2008). Fear of Pain, Pain Catastrophizing, and Acute Pain Perception: Relative Prediction and Timing of Assessment. *Journal of Pain*, *9*(9), 806–812. https://doi.org/10.1016/j.jpain.2008.03.012

Hobson, R. P. (2012). Autism, Literal Language and Concrete Thinking: Some Developmental Considerations. *Metaphor and Symbol*, *27*(1), 4–21.

https://doi.org/10.1080/10926488.2012.638814

Hoekstra, R. A., Bartels, M., Verweij, C. J. H., & Boomsma, D. I. (2007). Heritability of autistic traits in the general population. *Archives of Pediatrics and Adolescent Medicine*, *161*(4), 372–377. https://doi.org/10.1001/archpedi.161.4.372

Hollocks, M. J., Lerh, J. W., Magiati, I., Meiser-Stedman, R., & Brugha, T. S. (2019). Anxiety and depression in adults with autism spectrum disorder: A systematic review and meta-analysis. *Psychological Medicine*, *49*(4), 559–572. https://doi.org/10.1017/S0033291718002283

Horn, M. E., Alappattu, M. J., Gay, C. W., & Bishop, M. (2014). Fear of severe pain mediates sex differences in pain sensitivity responses to thermal stimuli. *Pain Research and Treatment*, *2014*. https://doi.org/10.1155/2014/897953

Huang, H., Nagao, M., Arita, H., Shiozawa, J., Nishio, H., Kobayashi, Y., Kaneko, H., Nagayama, M., Saita, Y., Ishijima, M., Takazawa, Y., Ikeda, H., & Kaneko, K. (2019). Reproducibility, responsiveness and validation of the Tampa Scale for Kinesiophobia in patients with ACL injuries. *Health and Quality of Life Outcomes*, *17*(1), 150. https://doi.org/10.1186/s12955-019-1217-7

Huang, H. W., Wang, W. C., & Lin, C. C. (2010). Influence of age on thermal thresholds, thermal pain thresholds, and reaction time. *Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia*, *17*(6), 722–726. https://doi.org/10.1016/J.JOCN.2009.10.003

Hurst, R. M., Mitchell, J. T., Kimbrel, N. A., Kwapil, T. K., & Nelson-Gray, R. O. (2007). Examination of the reliability and factor structure of the Autism Spectrum Quotient (AQ) in a non-clinical sample. *Personality and Individual Differences*, *43*(7), 1938–

1949. https://doi.org/10.1016/j.paid.2007.06.012

Iannetti, G. D., & Mouraux, A. (2010a). From the neuromatrix to the pain matrix (and back). *Experimental Brain Research*, *5*(1), 1–12. https://doi.org/10.1007/s00221-010-2340-1

IASP Terminology - IASP. (2017). https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698

Iggo, A. (1977). Cutaneous and Subcutaneous Sense Organs. *British Medical Bulletin*, *33*(2), 97–102. https://doi.org/10.1093/oxfordjournals.bmb.a071432

International Assosiation for the Study of Pain. (2020). *IASP Revised Definition of Pain*.

Inui, K., & Kakigi, R. (2012). Pain perception in humans: Use of intraepidermal electrical stimulation. In *Journal of Neurology, Neurosurgery and Psychiatry*, *83*(5), 551–556. https://doi.org/10.1136/jnnp-2011-301484

Irvine, E. (2021). The Role of Replication Studies in Theory Building: *Https://Doi.Org/10.1177/1745691620970558*, *16*(4), 844–853. https://doi.org/10.1177/1745691620970558

Irwin, R. J., & Whitehead, P. R. (1991). Towards an Objective Psychophysics of Pain. *Psychological Science*, *2*(4), 230–235. https://doi.org/10.1111/j.1467-9280.1991.tb00140.x

Izard, C. E., Huebner, R. R., Risser, D., & Dougherty, L. (1980). The young infant's ability to produce discrete emotion expressions. *Developmental Psychology*, *16*(2), 132–140. https://doi.org/10.1037/0012-1649.16.2.132

Jackson, T., Iezzi, T., Chen, H., Ebnet, S., & Eglitis, K. (2005). Gender, interpersonal

transactions, and the perception of pain: An experimental analysis. *Journal of Pain*, *6*(4), 228–236. https://doi.org/10.1016/j.jpain.2004.12.004

Jain, A., Spencer, D., Yang, W., Kelly, J. P., Newschaffer, C. J., Johnson, J., Marshall, J., Azocar, F., Tabb, L. P., & Dennen, T. (2014). Injuries among children with autism spectrum disorder. *Academic Pediatrics*, *14*(4), 390–397. https://doi.org/10.1016/j.acap.2014.03.012

Jensen, K., Andersen, H. Ø., Olesen, J., & Lindblom, U. (1986). Pressure-pain threshold in human temporal region. Evaluation of a new pressure algometer. *Pain*, *25*(3), 313–323. https://doi.org/10.1016/0304-3959(86)90235-6

Johnson, M. H. (2014). Autism: demise of the innate social orienting hypothesis. *Current Biology*, *24*(1). https://doi.org/10.1016/J.CUB.2013.11.021

Joshi, G., Wozniak, J., Petty, C., Martelon, M. K., Fried, R., Bolfek, A., Kotte, A., Stevens, J., Furtak, S. L., Bourgeois, M., Caruso, J., Caron, A., & Biederman, J. (2013). Psychiatric Comorbidity and Functioning in a Clinically Referred Population of Adults with Autism Spectrum Disorders: A Comparative Study. *Journal of Autism and Developmental Disorders*, *43*(6), 1314–1325. https://doi.org/10.1007/s10803-012-1679-5

Jovanovic, T, Norrholm, S. ., Fennell, J. ., Keyes, M., Fiallos, A. ., Myers, K. ., Davis, M., & Duncan, E. . (2009). Posttraumatic stress disorder may be associated with impaired fear inhibition: relation to symptom severity. *Psychiatry Research*, *167*(1–2), 151–160. https://doi.org/10.1016/J.PSYCHRES.2007.12.014

Jovanovic, Tanja, Kazama, A., Bachevalier, J., & Davis, M. (2012). Impaired Safety Signal Learning May be a Biomarker of PTSD. *Neuropharmacology*, *62*(2), 695.

https://doi.org/10.1016/J.NEUROPHARM.2011.02.023

Kaiser, M. D., Yang, D. Y.-J., Voos, A. C., Bennett, R. H., Gordon, I., Pretzsch, C., Beam, D., Keifer, C., Eilbott, J., McGlone, F., & Pelphrey, K. A. (2016). Brain Mechanisms for Processing Affective (and Nonaffective) Touch Are Atypical in Autism. *Cerebral Cortex*, *26*(6), 2705–2714. https://doi.org/10.1093/cercor/bhv125

Kanner, L. (1943). Autistic Disturbances of Affective Contact. *Pathology*, *2*, 217–250. http://www.neurodiversity.com/library_kanner_1943.pdf

Kapp, S. K., Steward, R., Crane, L., Elliott, D., Elphick, C., Pellicano, E., & Russell, G. (2019). 'People should be allowed to do what they like': Autistic adults' views and experiences of stimming. *Autism*, *23*(7), 1782–1792. https://doi.org/10.1177/1362361319829628

Karmiloff-Smith, A. (2006). The tortuous route from genes to behavior: A neuroconstructivist approach. *Cognitive, Affective and Behavioral Neuroscience*, *6*(1), 9–17. https://doi.org/10.3758/CABN.6.1.9

Karos, K., Alleva, J. M., & Peters, M. L. (2018). Pain, Please: An Investigation of Sampling Bias in Pain Research. *The Journal of Pain*, *19*(7), 787–796. https://doi.org/10.1016/J.JPAIN.2018.02.011

Karos, K., Meulders, A., Goubert, L., & Vlaeyen, J. W. S. (2020). Hide Your Pain: Social Threat Increases Pain Reports and Aggression, but Reduces Facial Pain Expression and Empathy. *The Journal of Pain*, *21*(3), 334–346. https://doi.org/https://doi.org/10.1016/j.jpain.2019.06.014

Karos, K., Williams, A. C. de C., Meulders, A., & Vlaeyen, J. W. S. (2018). Pain as a threat

to the social self: a motivational account. *Pain*, *159*(9). https://journals.lww.com/pain/Fulltext/2018/09000/Pain_as_a_threat_to_the_social_self__a.6.aspx

Kasari, C., Sigman, M., Mundy, P., & Yirmiya, N. (1990). Affective sharing in the context of joint attention interactions of normal, autistic, and mentally retarded children. *Journal of Autism and Developmental Disorders*, *20*(1), 87–100. https://doi.org/10.1007/BF02206859

Katz, J., & Melzack, R. (1999). Measurement of pain. *Surgical Clinics of North America*, *79*(2), 231–252. https://doi.org/10.1016/S0039-6109(05)70381-9

Kazamel, M., & Warren, P. P. (2017). History of electromyography and nerve conduction studies: A tribute to the founding fathers. *Journal of Clinical Neuroscience*, *43*, 54–60. https://doi.org/10.1016/j.jocn.2017.05.018

Kemper, C. J., Lutz, J., Bähr, T., Rüddel, H., & Hock, M. (2012). Construct Validity of the Anxiety Sensitivity Index–3 in Clinical Samples. *Assessment*, *19*(1), 89–100. https://doi.org/10.1177/1073191111429389

Kern, J. K., Trivedi, M. H., Garver, C. R., Grannemann, B. D., Andrews, A. A., Savla, J. S., Johnson, D. G., Mehta, J. A., & Schroeder, J. L. (2006). The pattern of sensory processing abnormalities in autism. *Autism*, *10*(5), 480–494. https://doi.org/10.1177/1362361306066564

Kerns, C. M., Winder-Patel, B., Iosif, A. M., Nordahl, C. W., Heath, B., Solomon, M., & Amaral, D. G. (2020). Clinically Significant Anxiety in Children with Autism Spectrum Disorder and Varied Intellectual Functioning. *Journal of Clinical Child and Adolescent Psychology*. https://doi.org/10.1080/15374416.2019.1703712

Ketelaars, C., Horwitz, E., Sytema, S., Bos, J., Wiersma, D., Minderaa, R., & Hartman, C. A. (2008). Brief Report: Adults with Mild Autism Spectrum Disorders (ASD): Scores on the Autism Spectrum Quotient (AQ) and Comorbid Psychopathology. *Journal of Autism and Developmental Disorders*, *38*(1), 176–180. https://doi.org/10.1007/s10803-007-0358-4

Kingdom, F. A. A., & Prins, N. (2016). *Psychophysics : a practical introduction*. Elsevier Academic Press.

Klein, D. N., & Riso, L. P. (1993). Psychiatric disorders: Problems of boundaries and comorbidity. In G. G. Costello (Ed.), *Basic issues in psychopathology.* (pp. 19–66). Guilford Press.

Klin, A., Sparrow, S. S., Marans, W. D., Carter, A., & Volkmar, F. R. (2000). Assessment issues in children and adolescents with Asperger syndrome. In A. Klin, F. R. Volkmar, & S. S. Sparrow (Eds.), *Asperger syndrome.* (pp. 309–339). The Guilford Press.

Klintwall, L., Holm, A., Eriksson, M., Carlsson, L. H., Olsson, M. B., Hedvall, Å., Gillberg, C., & Fernell, E. (2011). Sensory abnormalities in autism. A brief report. *Research in Developmental Disabilities*, *32*(2), 795–800. https://doi.org/10.1016/j.ridd.2010.10.021

Kloosterman, P. H., Keefer, K. V., Kelley, E. A., Summerfeldt, L. J., & Parker, J. D. A. (2011). Evaluation of the factor structure of the Autism-Spectrum Quotient. *Personality and Individual Differences*, *50*(2), 310–314. https://doi.org/10.1016/j.paid.2010.10.015

Koban, L., & Wager, T. D. (2016). Beyond conformity: Social influences on pain reports and physiology. *Emotion*, *16*(1), 24–32. https://doi.org/10.1037/emo0000087

Koltzenburg, M., Lundberg, L. E. R., & Torebjörk, H. E. (1992). Dynamic and static

components of mechanical hyperalgesia in human hairy skin. *Pain*, *51*(2), 207–219. https://doi.org/10.1016/0304-3959(92)90262-A

Kosek, E., & Lundberg, L. (2003). Segmental and plurisegmental modulation of pressure pain thresholds during static muscle contractions in healthy individuals. *European Journal of Pain*, *7*(3), 251–258. https://doi.org/10.1016/S1090-3801(02)00124-6

Krahé, C., Springer, A., Weinman, J. A., & Fotopoulou, A. (2013). The social modulation of pain: Others as predictive signals of salience - a systematic review. *Frontiers in Human Neuroscience*, *7*(JUL). https://doi.org/10.3389/fnhum.2013.00386

Kroenke, K. (2018). Pain measurement in research and practice. In *Journal of General Internal Medicine* (Vol. 33, pp. 7–8). Springer New York LLC. https://doi.org/10.1007/s11606-018-4363-4

Kroska, E. B. (2016). A meta-analysis of fear-avoidance and pain intensity: The paradox of chronic pain. *Scandinavian Journal of Pain*, *13*, 43–58. https://doi.org/10.1016/j.sjpain.2016.06.011

Kunz, M., Chatelle, C., Lautenbacher, S., & Rainville, P. (2008). The relation between catastrophizing and facial responsiveness to pain. *Pain*, *140*(1), 127–134. https://doi.org/10.1016/j.pain.2008.07.019

Kunz, M., Lautenbacher, S., LeBlanc, N., & Rainville, P. (2012). Are both the sensory and the affective dimensions of pain encoded in the face? *Pain*, *153*(2), 350–358. https://doi.org/10.1016/j.pain.2011.10.027

Kunz, M., Meixner, D., & Lautenbacher, S. (2019). Facial muscle movements encoding pain - A systematic review. In *Pain* (Vol. 160, Issue 3, pp. 535–549). Lippincott Williams

and Wilkins. https://doi.org/10.1097/j.pain.0000000000001424

Kuo, M. H., Orsmond, G. I., Coster, W. J., & Cohn, E. S. (2014). Media use among adolescents with autism spectrum disorder. *Autism*, *18*(8), 914–923. https://doi.org/10.1177/1362361313497832

LaChapelle, D. L., Hadjistavropoulos, T., & Kenneth, D. C. (1999). Pain measurement in persons with intellectual disabilities. *Clinical Journal of Pain*, *15*(1), 13–23. https://doi.org/10.1097/00002508-199903000-00004

Lai, M. C., Lombardo, M. V., Chakrabarti, B., & Baron-Cohen, S. (2013). Subgrouping the Autism "Spectrum": Reflections on DSM-5. *PLoS Biology*, *11*(4). https://doi.org/10.1371/journal.pbio.1001544

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in Psychology*, *0*(NOV), 863. https://doi.org/10.3389/FPSYG.2013.00863

Lam, K. S. L., & Aman, M. G. (2007). The repetitive behavior scale-revised: Independent validation in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *37*(5), 855–866. https://doi.org/10.1007/s10803-006-0213-z

Landry, O., & Chouinard, P. A. (2016). Why We Should Study the Broader Autism Phenotype in Typically Developing Populations. *Journal of Cognition and Development*, *17*(4), 584–595. https://doi.org/10.1080/15248372.2016.1200046

Larsson, C., Ekvall Hansson, E., Sundquist, K., & Jakobsson, U. (2016). Kinesiophobia and its relation to pain characteristics and cognitive affective variables in older adults with chronic pain. *BMC Geriatrics*, *16*(1). https://doi.org/10.1186/s12877-016-0302-6

Lau, W. Y. P., Kelly, A. B., & Peterson, C. C. (2013). Further Evidence on the Factorial Structure of the Autism Spectrum Quotient (AQ) for Adults With and Without a Clinical Diagnosis of Autism. *Journal of Autism and Developmental Disorders*, *43*(12), 2807–2815. https://doi.org/10.1007/s10803-013-1827-6

Lautenbacher, S., Bär, K.-J., Eisold, P., & Kunz, M. (2017). Understanding Facial Expressions of Pain in Patients With Depression. *The Journal of Pain*, *18*(4), 376–384. https://doi.org/10.1016/J.JPAIN.2016.11.011

Lawson, K., Reesor, K. A., Keefe, F. J., & Turner, J. A. (1990). Dimensions of pain-related cognitive coping: cross-validation of the factor structure of the Coping Strategy Questionnaire. *Pain*, *43*(2), 195–204. https://doi.org/10.1016/0304-3959(90)91073-R

Lee, J. E., Kahana, B., & Kahana, E. (2016). Social support and cognitive functioning as resources for elderly persons with chronic arthritis pain. *Aging and Mental Health*, *20*(4), 370–379. https://doi.org/10.1080/13607863.2015.1013920

Lee, J. J., Kim, H. J., Čeko, M., Park, B. yong, Lee, S. A., Park, H., Roy, M., Kim, S. G., Wager, T. D., & Woo, C. W. (2021). A neuroimaging biomarker for sustained experimental and clinical pain. *Nature Medicine*, *27*(1), 174–182. https://doi.org/10.1038/s41591-020-1142-7

Lee, R. C., Zhang, D., & Hannig, J. (2000). Biophysical Injury Mechanisms in Electrical Shock Trauma. *Annual Review of Biomedical Engineering*, *2*(1), 477–509. https://doi.org/10.1146/annurev.bioeng.2.1.477

Leekam, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2007). Describing the Sensory Abnormalities of Children and Adults with Autism. *Journal of Autism and Developmental Disorders*, *37*(5), 894–910. https://doi.org/10.1007/s10803-006-0218-7

5714 Leekam, S. R., Prior, M. R., & Uljarevic, M. (2011). Restricted and repetitive behaviors in
5715 autism spectrum disorders: A review of research in the last decade. *Psychological*
5716 *Bulletin*, *137*(4), 562–593. https://doi.org/10.1037/a0023341

5717 Legrain, V., Mancini, F., Sambo, C. F., Torta, D. M., Ronga, I., & Valentini, E. (2012).
5718 Cognitive aspects of nociception and pain. Bridging neurophysiology with cognitive
5719 psychology. *Neurophysiologie Clinique/Clinical Neurophysiology*, *42*(5), 325–336.
5720 https://doi.org/https://doi.org/10.1016/j.neucli.2012.06.003

5721 Leo, K. (1943). Autistic disturbances of affective contact.pdf. In *Nervous Child* (Vol. 2, pp.
5722 217–250).

5723 Leppink, J. (2018). Analysis of Covariance (ANCOVA) vs. Moderated Regression
5724 (MODREG): Why the Interaction Matters. *Health Professions Education*, *4*(3), 225–
5725 232. https://doi.org/10.1016/J.HPE.2018.04.001

5726 LeResche, L. (1982). Facial expression in pain: A study of candid photographs. *Journal of*
5727 *Nonverbal Behavior*, *7*(1), 46–56. https://doi.org/10.1007/BF01001777

5728 LeResche, L., & Dworkin, S. F. (1988). Facial expressions of pain and emotions in chronic
5729 TMD patients. *Pain*, *35*(1), 71–78. https://doi.org/10.1016/0304-3959(88)90278-3

5730 Letz, R., & Gerr, F. (1994). Covariates of human peripheral nerve function: I. Nerve
5731 conduction velocity and amplitude. *Neurotoxicology and Teratology*, *16*(1), 95–104.
5732 https://doi.org/10.1016/0892-0362(94)90014-0

5733 Leung, L. (2012). Pain Catastrophizing: An Updated Review. *Indian Journal of*
5734 *Psychological Medicine*, *34*(3), 204. https://doi.org/10.4103/0253-7176.106012

5735 Levenstein, S., & Kaplan, G. A. (1998). Socioeconomic status and ulcer: A prospective study

of contributory risk factors. *Journal of Clinical Gastroenterology*, *26*(1), 14–17. https://doi.org/10.1097/00004836-199801000-00005

Levy, J., Goldstein, A., Pratt, M., & Feldman, R. (2018). Maturation of pain empathy from child to adult shifts from single to multiple neural rhythms to support interoceptive representations. *Scientific Reports*, *8*(1), 1810. https://doi.org/10.1038/s41598-018-19810-3

Lewin, G. R., & Moshourab, R. (2004). Mechanosensation and pain. *Journal of Neurobiology*, *61*(1), 30–44. https://doi.org/10.1002/NEU.20078

Li, J., Simone, D. A., & Larson, A. A. (1999). Windup leads to characteristics of central sensitization. *Pain*, *79*(1), 75–82. https://doi.org/10.1016/S0304-3959(98)00154-7

Li, L., Rutlin, M., Abraira, V. E., Cassidy, C., Kus, L., Gong, S., Jankowski, M. P., Luo, W., Heintz, N., Koerber, H. R., Woodbury, C. J., & Ginty, D. D. (2011). The Functional Organization of Cutaneous Low-Threshold Mechanosensory Neurons. *Cell*, *147*(7), 1615–1627. https://doi.org/10.1016/J.CELL.2011.11.027

Liljencrantz, J., Björnsdotter, M., Morrison, I., Bergstrand, S., Ceko, M., Seminowicz, D. A., Cole, J., Bushnell, M. C., & Olausson, H. (2013). Altered C-tactile processing in human dynamic tactile allodynia. *Pain*, *154*(2), 227–234. https://doi.org/10.1016/J.PAIN.2012.10.024

Lindsay, G. W. (2020). Attention in Psychology, Neuroscience, and Machine Learning. *Frontiers in Computational Neuroscience*, *0*, 29. https://doi.org/10.3389/FNCOM.2020.00029

Lipsker, C. W., Bölte, S., Hirvikoski, T., Lekander, M., Holmström, L., & Wicksell, R. K.

(2018). Prevalence of autism traits and attention-deficit hyperactivity disorder symptoms in a clinical sample of children and adolescents with chronic pain. *Journal of Pain Research*, *11*, 2827–2836. https://doi.org/10.2147/JPR.S177534

Lipsker, C. W., von Heijne, M., Bölte, S., & Wicksell, R. K. (2018). A case report and literature review of autism and attention deficit hyperactivity disorder in paediatric chronic pain. *Acta Paediatrica*, *107*(5), 753–758. https://doi.org/10.1111/apa.14220

Lissek, S., Powers, A. S., McClure, E. B., Phelps, E. A., Woldehawariat, G., Grillon, C., & Pine, D. S. (2005). Classical fear conditioning in the anxiety disorders: a meta-analysis. *Behaviour Research and Therapy*, *43*(11), 1391–1424. https://doi.org/10.1016/J.BRAT.2004.10.007

Loades, M. E. (2015). Evidence-Based Practice in the Face of Complexity and Comorbidity: A Case Study of an Adolescent With Asperger's Syndrome, Anxiety, Depression, and Chronic Pain. *Journal of Child and Adolescent Psychiatric Nursing*, *28*(2), 73–83. https://doi.org/10.1111/jcap.12108

Loeser, J. D. (1980). Perspectives on Pain. *Clinical Pharmacology & Therapeutics*, 313–316. https://doi.org/10.1007/978-1-349-05952-2_34

Loeser, J. D. (2012). Chronic Pain Is More Than a Peripheral Event. *The Journal of Pain*, *13*(10), 930–931. https://doi.org/10.1016/J.JPAIN.2012.07.002

Loeser, J. D., & Melzack, R. (1999). Pain: An overview. *Lancet*, *353*(9164), 1607–1609. Elsevier Limited. https://doi.org/10.1016/S0140-6736(99)01311-2

Loeser, J. D., & Treede, R. D. (2008). The Kyoto protocol of IASP Basic Pain Terminology. *Pain*, *137*(3), 473–477. https://doi.org/10.1016/j.pain.2008.04.025

Loggia, M. L., Mogil, J. S., & Bushnell, M. C. (2008). Experimentally Induced Mood Changes Preferentially Affect Pain Unpleasantness. *Journal of Pain*, *9*(9), 784–791. https://doi.org/10.1016/j.jpain.2008.03.014

López-Martínez, A. E., Esteve-Zarazaga, R., & Ramírez-Maestre, C. (2008). Perceived Social Support and Coping Responses Are Independent Variables Explaining Pain Adjustment Among Chronic Pain Patients. *Journal of Pain*, *9*(4), 373–379. https://doi.org/10.1016/j.jpain.2007.12.002

Lourenço, O. M. (2016). Developmental stages, Piagetian stages in particular: A critical review. *New Ideas in Psychology*, *40*, 123–137. https://doi.org/10.1016/j.newideapsych.2015.08.002

Low Kapalu, C. M., Hall, J. J., & Wallace, D. P. (2018). Neuropsychological Functioning of Youth Receiving Intensive Interdisciplinary Pain Treatment. *Journal of Pediatric Psychology*, *43*(8), 870–881. https://doi.org/10.1093/jpepsy/jsy034

Lumpkin, E. A., & Caterina, M. J. (2007). Mechanisms of sensory transduction in the skin. *Nature*, *445*(7130), 858–865. https://doi.org/10.1038/nature05662

Lumpkin, E. A., Marshall, K. L., & Nelson, A. M. (2010). The cell biology of touch. *The Journal of Cell Biology*, *191*(2), 237–248. https://doi.org/10.1083/jcb.201006074

Lundqvist, L.-O., & Lindner, H. (2017). Is the Autism-Spectrum Quotient a Valid Measure of Traits Associated with the Autism Spectrum? A Rasch Validation in Adults with and Without Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *47*(7), 2080–2091. https://doi.org/10.1007/s10803-017-3128-y

Lyall, K., Croen, L., Daniels, J., Fallin, M. D., Ladd-Acosta, C., Lee, B. K., Park, B. Y.,

Snyder, N. W., Schendel, D., Volk, H., Windham, G. C., & Newschaffer, C. (2017). The Changing Epidemiology of Autism Spectrum Disorders. *Annual Review of Public Health*, *38*, 81–102. https://doi.org/10.1146/annurev-publhealth-031816-044318

Lynam, D. R., Hoyle, R. H., & Newman, J. P. (2006). The perils of partialling: cautionary tales from aggression and psychopathy. *Assessment*, *13*(3), 328–341. https://doi.org/10.1177/1073191106290562

MacDonald, G., & Leary, M. R. (2005). Why does social exclusion hurt? The relationship between social and physical pain. In *Psychological Bulletin*, *131*(2), 202–223. https://doi.org/10.1037/0033-2909.131.2.202

Magerl, W., & Klein, T. (2006). Chapter 33 Experimental human models of neuropathic pain. *Handbook of Clinical Neurology*, *81*, 503–516. https://doi.org/10.1016/S0072-9752(06)80037-0

Magerl, W., Krumova, E. K., Baron, R., Tölle, T., Treede, R.-D., & Maier, C. (2010). Reference data for quantitative sensory testing (QST): Refined stratification for age and a novel method for statistical comparison of group data. *Pain*, *151*(3), 598–605. https://doi.org/https://doi.org/10.1016/j.pain.2010.07.026

Magerl, W., Wilk, S. H., & Treede, R.-D. (1998). Secondary hyperalgesia and perceptual wind-up following intradermal injection of capsaicin in humans. *Pain*, *74*(2–3), 257–268. https://doi.org/10.1016/S0304-3959(97)00177-2

Magiati, I., Charman, T., & Howlin, P. (2007). A two-year prospective follow-up study of community-based early intensive behavioural intervention and specialist nursery provision for children with autism spectrum disorders. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *48*(8), 803–812. https://doi.org/10.1111/j.1469-

7610.2007.01756.x

Mahler, B., Carlsson, S., Andersson, T., & Tomson, T. (2018). Risk for injuries and accidents in epilepsy. *Neurology*, *90*(9), e779 LP-e789. https://doi.org/10.1212/WNL.0000000000005035

Mahler, M. S. (1952). On Child Psychosis and Schizophrenia. *The Psychoanalytic Study of the Child*, *7*(1), 286–305. https://doi.org/10.1080/00797308.1952.11823164

Maier, C., Baron, R., Tölle, T. R., Binder, A., Birbaumer, N., Birklein, F., Gierthmühlen, J., Flor, H., Geber, C., Huge, V., Krumova, E. K., Landwehrmeyer, G. B., Magerl, W., Maihöfner, C., Richter, H., Rolke, R., Scherens, A., Schwarz, A., Sommer, C., … Treede, R.-D. (2010). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain*, *150*(3), 439–450. https://doi.org/https://doi.org/10.1016/j.pain.2010.05.002

Mandell, D. S., Novak, M. M., & Zubritsky, C. D. (2005). Factors Associated With Age of Diagnosis Among Children With Autism Spectrum Disorders. *Pediatrics*, *116*(6), 1480 LP – 1486. https://doi.org/10.1542/peds.2005-0185

Marchettini, P. (1993). Muscle pain: Animal and human experimental and clinical studies. *Muscle & Nerve*, *16*(10), 1033–1039. https://doi.org/10.1002/mus.880161006

Marco, E. J., Hinkley, L. B. N., Hill, S. S., & Nagarajan, S. S. (2011). Sensory Processing in Autism: A Review of Neurophysiologic Findings. *Pediatric Research*, *69*(8), 48–54. https://doi.org/10.1203/PDR.0b013e3182130c54

Martel, M. O., Wasan, A. D., & Edwards, R. R. (2013). Sex differences in the stability of

conditioned pain modulation (cpm) among patients with chronic pain. *Pain Medicine (United States)*, *14*(11), 1757–1768. https://doi.org/10.1111/pme.12220

Martínez-González, A. E., & Piqueras, J. A. (2018). Validation of the Repetitive Behavior Scale-Revised in Spanish-Speakers Participants with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *48*(1), 198–208. https://doi.org/10.1007/s10803-017-3276-0

Masi, A., Demayo, M. M., Glozier, N., & Guastella, A. J. (2017). An Overview of Autism Spectrum Disorder, Heterogeneity and Treatment Options. *Neuroscience Bulletin*, *33*. https://doi.org/10.1007/s12264-017-0100-y

Master, S. L., Eisenberger, N. I., Taylor, S. E., Naliboff, B. D., Shirinyan, D., & Lieberman, M. D. (2009). A picture's worth: Partner photographs reduce experimentally induced pain. *Psychological Science*, *20*(11), 1316–1318. https://doi.org/10.1111/j.1467-9280.2009.02444.x

Mazurek, M. O. (2013). Social media use among adults with autism spectrum disorders. *Computers in Human Behavior*, *29*(4), 1709–1714. https://doi.org/10.1016/j.chb.2013.02.004

Mazurek, M. O., Keefer, A., Shui, A., & Vasa, R. A. (2014). One-year course and predictors of abdominal pain in children with autism spectrum disorders: The role of anxiety and sensory over-responsivity. *Research in Autism Spectrum Disorders*, *8*(11), 1508–1515. https://doi.org/10.1016/J.RASD.2014.07.018

McCracken, L. M., Zayfert, C., & Gross, R. T. (1992). The pain anxiety symptoms scale: development and validation of a scale to measure fear of pain. *Pain*, *50*(1), 67–73. https://doi.org/10.1016/0304-3959(92)90113-P

McElhanon, B. O., McCracken, C., Karpen, S., & Sharp, W. G. (2014). Gastrointestinal Symptoms in Autism Spectrum Disorder: A Meta-analysis. *Pediatrics*, *133*(5), 872 LP – 883. https://doi.org/10.1542/peds.2013-3995

McGlone, F., & Reilly, D. (2010). The cutaneous sensory system. *Neuroscience & Biobehavioral Reviews*, *34*(2), 148–159. https://doi.org/10.1016/J.NEUBIOREV.2009.08.004

McGlone, F., Wessberg, J., & Olausson, H. (2014). Discriminative and Affective Touch: Sensing and Feeling. In *Neuron* (Vol. 82, Issue 4, pp. 737–755). Cell Press. https://doi.org/10.1016/j.neuron.2014.05.001

McGrath, P. J., Rosmus, C., Canfield, C., Campbell, M. A., & Hennigar, A. (2008). Behaviours caregivers use to determine pain in non-verbal, cognitively impaired individuals. *Developmental Medicine & Child Neurology*, *40*(5), 340–343. https://doi.org/10.1111/j.1469-8749.1998.tb15386.x

McIntosh, D. N., Reichmann-Decker, A., Winkielman, P., & Wilbarger, J. L. (2006). When the social mirror breaks: Deficits in automatic, but not voluntary, mimicry of emotional facial expressions in autism. *Developmental Science*, *9*(3), 295–302. https://doi.org/10.1111/j.1467-7687.2006.00492.x

McNeil, D. W., & Rainwater, A. J. (1998). Development of the fear of pain questionnaire - III. *Journal of Behavioral Medicine*, *21*(4), 389–410. https://doi.org/10.1023/A:1018782831217

McPartland, J. C., Crowley, M. J., Perszyk, D. R., Mukerji, C. E., Naples, A. J., Wu, J., & Mayes, L. C. (2012). Preserved reward outcome processing in ASD as revealed by event-related potentials. *Journal of Neurodevelopmental Disorders*, *4*(1), 16.

https://doi.org/10.1186/1866-1955-4-16

Meier, S. M., Petersen, L., Schendel, D. E., Mattheisen, M., Mortensen, P. B., & Mors, O. (2015). Obsessive-Compulsive Disorder and Autism Spectrum Disorders: Longitudinal and Offspring Risk. *PloS One*, *10*(11), e0141703–e0141703. https://doi.org/10.1371/journal.pone.0141703

Melia, M., Schmidt, M., Geissler, B., König, J., Krahn, U., Ottersbach, H. J., Letzel, S., & Muttray, A. (2015). Measuring mechanical pain: The refinement and standardization of pressure pain threshold measurements. *Behavior Research Methods*, *47*(1), 216–227. https://doi.org/10.3758/s13428-014-0453-3

Melzack, R., Wall, P. D. (Patrick D., & Melzack, R. (1982). *The challenge of pain*. Penguin Books. https://books.google.co.uk/books/about/The_challenge_of_pain.html?id=_JBQlfeb1cIC&redir_esc=y

Mense, S. (1993). Nociception from skeletal muscle in relation to clinical muscle pain. *Pain*, *54*(3), 241–289. https://doi.org/10.1016/0304-3959(93)90027-m

Mercer, K., & Glenn, S. (2004). The expression of pain in infants with developmental delays. *Child: Care, Health and Development*, *30*(4), 353–360. https://doi.org/10.1111/j.1365-2214.2004.00430.x

Merskey, H. (Ed.). (1986). Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. *Pain, Suppl 3*, 226.

Messmer, R. L., Nader, R., & Craig, K. D. (2008). Brief report: Judging pain intensity in children with autism undergoing venepuncture: The influence of facial activity. *Journal*

5915 *of Autism and Developmental Disorders*, *38*(7), 1391–1394.
5916 https://doi.org/10.1007/s10803-007-0511-0

5917 Meulders, A., Vansteenwegen, D., & Vlaeyen, J. W. S. (2011). The acquisition of fear of
5918 movement-related pain and associative learning: A novel pain-relevant human fear
5919 conditioning paradigm. *PAIN*, *152*(11).
5920 https://journals.lww.com/pain/Fulltext/2011/11000/The_acquisition_of_fear_of_movem
5921 ent_related_pain.7.aspx

5922 Meulders, A., & Vlaeyen, J. W. S. (2012). Reduction of fear of movement-related pain and
5923 pain-related anxiety: An associative learning approach using a voluntary movement
5924 paradigm. *PAIN*, *153*(7).
5925 https://journals.lww.com/pain/Fulltext/2012/07000/Reduction_of_fear_of_movement_re
5926 lated_pain_and.25.aspx

5927 Meulders, A., & Vlaeyen, J. W. S. (2013). The acquisition and generalization of cued and
5928 contextual pain-related fear: An experimental study using a voluntary movement
5929 paradigm. *PAIN*, *154*(2), 272–282.
5930 https://doi.org/https://doi.org/10.1016/j.pain.2012.10.025

5931 Meyer, K., Sprott, H., & Mannion, A. F. (2008). Cross-cultural adaptation, reliability, and
5932 validity of the German version of the Pain Catastrophizing Scale. *Journal of*
5933 *Psychosomatic Research*, *64*(5), 469–478.
5934 https://doi.org/10.1016/j.jpsychores.2007.12.004

5935 Meyer, R. A., Ringkamp, M., Campbell, J. N., & Raja, S. N. (2006). Peripheral mechanisms
5936 of cutaneous nociception. In *Wall and Melzack's Textbook of Pain* (pp. 3–34). Elsevier.
5937 https://doi.org/10.1016/b0-443-07287-6/50006-0

Mihailov, A., Philippe, C., Gloaguen, A., Grigis, A., Laidi, C., Piguet, C., Houenou, J., & Frouin, V. (2020). Cortical signatures in behaviorally clustered autistic traits subgroups: a population-based study. *Translational Psychiatry*, *10*(1), 1–12. https://doi.org/10.1038/s41398-020-00894-3

Milad, M. R., Pitman, R. K., Ellis, C. B., Gold, A. L., Shin, L. M., Lasko, N. B., Zeidan, M. A., Handwerger, K., Orr, S. P., & Rauch, S. L. (2009). Neurobiological Basis of Failure to Recall Extinction Memory in Posttraumatic Stress Disorder. *Biological Psychiatry*, *66*(12), 1075–1082. https://doi.org/10.1016/J.BIOPSYCH.2009.06.026

Miles, J. (2003). A framework for power analysis using a structural equation modelling procedure. *BMC Medical Research Methodology*, *3*(1), 1–11. https://doi.org/10.1186/1471-2288-3-27

Militerni, R., Bravaccio, C., Falco, C., Puglisi-Allegra, S., Pascucci, T., & Fico, C. (2000). Pain reactivity in children with autistic disorder. *The Journal of Headache and Pain*, *1*(1), 53–56. https://doi.org/10.1007/s101940050011

Miljković, A., Stipčić, A., Braš, M. B., Đorđević, V. B., Brajković, L. B., Hayward, C. B., Pavić BCDE, A., Kolčić ABCDEFG, I., & Polašek, O. (2014). *Is experimentally induced pain associated with socioeconomic status? Do poor people hurt more?* https://doi.org/10.12659/MSM.890714

Millan, M. J. (1999). The induction of pain: an integrative review. *Progress in Neurobiology*, *57*(1), 1–164. https://doi.org/10.1016/S0301-0082(98)00048-3

Minshawi, N. F., Hurwitz, S., Fodstad, J. C., Biebl, S., Morriss, D. H., & McDougle, C. J. (2014). The association between self-injurious behaviors and autism spectrum disorders. *Psychology Research and Behavior Management*, *7*, 125–136.

https://doi.org/10.2147/PRBM.S44635

Minshew, N. J., & Hobson, J. A. (2008). Sensory Sensitivities and Performance on Sensory Perceptual Tasks in High-functioning Individuals with Autism. *Journal of Autism and Developmental Disorders*, *38*(8), 1485–1498. https://doi.org/10.1007/s10803-007-0528-4

Miron, D., Duncan, G. H., & Catherine Bushnell, M. (1989). Effects of attention on the intensity and unpleasantness of thermal pain. *Pain*, *39*(3), 345–352. https://doi.org/10.1016/0304-3959(89)90048-1

Mitchell, L. A., MacDonald, R. A. R., & Brodie, E. E. (2004). Temperature and the cold pressor test. *The Journal of Pain : Official Journal of the American Pain Society*, *5*(4), 233–237. https://doi.org/10.1016/j.jpain.2004.03.004

Mitchell, S., Brian, J., Zwaigenbaum, L., Roberts, W., Szatmari, P., Smith, I., & Bryson, S. (2006). Early Language and Communication Development of Infants Later Diagnosed with Autism Spectrum Disorder. *Journal of Developmental & Behavioral Pediatrics*, *27*(2). https://journals.lww.com/jrnldbp/Fulltext/2006/04002/Early_Language_and_Communication_Development_of.4.aspx

Moayyeri, A., Soltani, A., Moosapour, H., & Raza, M. (2011). Evidence-based history taking under "time constraint." *Journal of Research in Medical Sciences : The Official Journal of Isfahan University of Medical Sciences*, *16*(4), 559–564. https://pubmed.ncbi.nlm.nih.gov/22091274

Mogil, J. S. (2015). Social modulation of and by pain in humans and rodents. *Pain*, *156*, S35–S41. https://doi.org/10.1097/01.j.pain.0000460341.62094.77

5984 Moloney, N. A., Hall, T. M., & Doody, C. M. (2012). Reliability of thermal quantitative
5985 sensory testing: A systematic review. *Journal of Rehabilitation Research and*
5986 *Development*, *49*(2), 191–208. https://doi.org/10.1682/JRRD.2011.03.0044

5987 Moore, D. J. (2015). Acute pain experience in individuals with autism spectrum disorders: A
5988 review. *Autism*, *19*(4), 387–399. https://doi.org/10.1177/1362361314527839

5989 Moore, D. J., Keogh, E., Crombez, G., & Eccleston, C. (2013). Methods for studying
5990 naturally occurring human pain and their analogues. *Pain*, *154*(2), 190–199.
5991 https://doi.org/10.1016/j.pain.2012.07.016

5992 Moore, D. J., Keogh, E., & Eccleston, C. (2012). The interruptive effect of pain on attention.
5993 *Quarterly Journal of Experimental Psychology*, *65*(3), 565–586.
5994 https://doi.org/10.1080/17470218.2011.626865

5995 Moreno, M. A., Waite, A., Pumper, M., Colburn, T., Holm, M., & Mendoza, J. (2017).
5996 Recruiting Adolescent Research Participants: In-Person Compared to Social Media
5997 Approaches. *Cyberpsychology, Behavior, and Social Networking*, *20*(1), 64–67.
5998 https://doi.org/10.1089/cyber.2016.0319

5999 Morey, R. A., Dunsmoor, J. E., Haswell, C. C., Brown, V. M., Vora, A., Weiner, J.,
6000 Stjepanovic, D., Wagner, H. R., & LaBar, K. S. (2015). Fear learning circuitry is biased
6001 toward generalization of fear associations in posttraumatic stress disorder. *Translational*
6002 *Psychiatry 2015 5:12*, *5*(12), e700–e700. https://doi.org/10.1038/tp.2015.196

6003 Mücke, M., Cuhls, H., Radbruch, L., Baron, R., Maier, C., Tölle, T., Treede, R.-D., & Rolke,
6004 R. (2014). Quantitative sensorische Testung. *Der Schmerz*, *28*(6), 635–648.
6005 https://doi.org/10.1007/s00482-014-1485-4

6006 Murray, A. L., Booth, T., McKenzie, K., Kuenssberg, R., & O'Donnell, M. (2014). Are
6007 autistic traits measured equivalently in individuals with and without an autism spectrum
6008 disorder? an invariance analysis of the autism spectrum quotient short form. *Journal of*
6009 *Autism and Developmental Disorders*, *44*(1), 55–64. https://doi.org/10.1007/s10803-
6010 013-1851-6

6011 Murray, G. K., Jones, P. B., Kuh, D., & Richards, M. (2007). Infant developmental
6012 milestones and subsequent cognitive function. *Annals of Neurology*, *62*(2), 128–136.
6013 https://doi.org/10.1002/ana.21120

6014 Muskat, B., Burnham Riosa, P., Nicholas, D. B., Roberts, W., Stoddart, K. P., &
6015 Zwaigenbaum, L. (2014). Autism comes to the hospital: The experiences of patients
6016 with autism spectrum disorder, their parents and health-care providers at two Canadian
6017 paediatric hospitals. *Autism*, *19*(4), 482–490.
6018 https://doi.org/10.1177/1362361314531341

6019 Myhre, M. C., Thoresen, S., Grøgaard, J. B., & Dyb, G. (2012). Familial factors and child
6020 characteristics as predictors of injuries in toddlers: A prospective cohort study. *British*
6021 *Medical Journal Open*, *2*(2). https://doi.org/10.1136/bmjopen-2011-000740

6022 Nader, R., Oberlander, T. F., Chambers, C. T., & Craig, K. D. (2004). Expression of Pain in
6023 Children With Autism. *The Clinical Journal of Pain*, *20*(2), 88–97.
6024 https://doi.org/10.1097/00002508-200403000-00005

6025 Nafe, J. P. (2007). The Pressure, Pain, and Temperature Senses. In *A handbook of general*
6026 *experimental psychology.* (pp. 1037–1087). Clark University Press.
6027 https://doi.org/10.1037/11374-019

6028 Nemiah, J. C., Freyberger, H., & Sifneos, P. E. (1976). Alexithymia: a view of the

psychosomatic process. In O. W. Hill (Ed.), *Modern trends in psychosomatic medicine* (pp. 430–439).

Neumann, D., Spezio, M. L., Piven, J., & Adolphs, R. (2006). Looking you in the mouth: abnormal gaze in autism resulting from impaired top-down modulation of visual attention. *Social Cognitive and Affective Neuroscience*, *1*(3), 194–202. https://doi.org/10.1093/scan/nsl030

Ng, K. K. W., Olausson, C., Vickery, R. M., & Birznieks, I. (2020). Temporal patterns in electrical nerve stimulation: Burst gap code shapes tactile frequency perception. *PLOS ONE*, *15*(8), e0237440. https://doi.org/10.1371/journal.pone.0237440

Nir, R. R., & Yarnitsky, D. (2015). Conditioned pain modulation. *Current Opinion in Supportive and Palliative Care*, *9*(2), 131–137. https://doi.org/10.1097/SPC.0000000000000126

Norrholm, S. D., & Jovanovic, T. (2018). Fear Processing, Psychophysiology, and PTSD. *Harvard Review of Psychiatry*, *26*(3), 129–141. https://doi.org/10.1097/HRP.0000000000000189

Nosek, B. A., & Errington, T. M. (2020). What is replication? *PLOS Biology*, *18*(3), e3000691. https://doi.org/10.1371/JOURNAL.PBIO.3000691

O'Connor, K. (1990). Towards a process paradigm in psychophysiology. *International Journal of Psychophysiology*, *9*(3), 209–223. https://doi.org/10.1016/0167-8760(90)90053-G

O'Neill, J., Brock, C., Olesen, A. E., Andresen, T., Nilsson, M., & Dickenson, A. H. (2012). Unravelling the mystery of capsaicin: A tool to understand and treat pain. In

Pharmacological Reviews, *64*(4), 939–971. American Society for Pharmacology and Experimental Therapeutics. https://doi.org/10.1124/pr.112.006163

O'Neill, M., & Jones, R. S. P. (1997). Sensory-perceptual abnormalities in autism: A case for more research? *Journal of Autism and Developmental Disorders*, *27*(3), 283–294. https://doi.org/10.1023/A:1025850431170

Oberlander, T. F., Gilbert, C. A., Chambers, C. T., O'Donnell, M. E., & Craig, K. D. (1999). Biobehavioral Responses to Acute Pain in Adolescents with a Significant Neurologic Impairment. *The Clinical Journal of Pain*, *15*(3), 201–209. https://doi.org/10.1097/00002508-199909000-00007

Oberman, L. M., Winkielman, P., & Ramachandran, V. S. (2009). Slow echo: Facial EMG evidence for the delay of spontaneous, but not voluntary, emotional mimicry in children with autism spectrum disorders. *Developmental Science*, *12*(4), 510–520. https://doi.org/10.1111/j.1467-7687.2008.00796.x

Ocañez, K. L. S., Kathryn McHugh, R., & Otto, M. W. (2010). A meta-analytic review of the association between anxiety sensitivity and pain. *Depression and Anxiety*, *27*(8), 760–767. https://doi.org/10.1002/da.20681

Ochoa, J. L., & Yarnitsky, D. (1993). Mechanical hyperalgesias in neuropathic pain patients: Dynamic and static subtypes. *Annals of Neurology*, *33*(5), 465–472. https://doi.org/10.1002/ana.410330509

Oller, D. K., Niyogi, P., Gray, S., Richards, J. A., Gilkerson, J., Xu, D., Yapanel, U., & Warren, S. F. (2010). Automated vocal analysis of naturalistic recordings from children with autism, language delay, and typical development. *Proceedings of the National Academy of Sciences*, *107*(30), 13354–13359.

https://doi.org/10.1073/PNAS.1003882107

Olof Dahlgren, S., & Gillberg, C. (1989). Symptoms in the first two years of life. *European Archives of Psychiatry and Neurological Sciences*, *238*(3), 169–174. https://doi.org/10.1007/BF00451006

Osman, A., Barrios, F. X., Kopper, B. A., Hauptmann, W., Jones, J., & O'Neill, E. (1997). Factor structure, reliability, and validity of the pain catastrophizing scale. *Journal of Behavioral Medicine*, *20*(6), 589–605. https://doi.org/10.1023/A:1025570508954

Osman, A., Breitenstein, J. L., Barrios, F. X., Gutierrez, P. M., & Kopper, B. A. (2002). The Fear of Pain Questionnaire-III: Further Reliability and Validity with Nonclinical Samples. *Journal of Behavioral Medicine*, *25*(2), 155–173. https://doi.org/10.1023/A:1014884704974

Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. *The Journal of Clinical Investigation*, *120*(11), 3779–3787. https://doi.org/10.1172/JCI43766

Ozand, P. T., Al-Odaib, A., Merza, H., & Al Harbi, S. (2003). Autism: A review. *Journal of Pediatric Neurology*, *1*(2), 55–67.

Parker, J. D. A., Taylor, G. J., & Bagby, R. M. (2003). The 20-Item Toronto Alexithymia Scale: III. Reliability and factorial validity in a community population. *Journal of Psychosomatic Research*, *55*(3), 269–275. https://doi.org/10.1016/S0022-3999(02)00578-0

Patrick, C. J., Craig, K. D., & Prkachin, K. M. (1986). Observer judgments of acute pain: Facial action determinants. *Journal of Personality and Social Psychology*, *50*(6), 1291–1298. https://doi.org/10.1037//0022-3514.50.6.1291

6096 Peacock, S., & Patel, S. (2008). Cultural Influences on Pain. *Reviews in Pain*, *1*(2), 6–9.
6097 https://doi.org/10.1177/204946370800100203

6098 Peerdeman, K. J., van Laarhoven, A. I. M., Peters, M. L., & Evers, A. W. M. (2016). An
6099 Integrative Review of the Influence of Expectancies on Pain. *Frontiers in Psychology*, *7*,
6100 1270. https://doi.org/10.3389/fpsyg.2016.01270

6101 Pelphrey, K. A., Sasson, N. J., Reznick, J. S., Paul, G., Goldman, B. D., & Piven, J. (2002).
6102 Visual Scanning of Faces in Autism. *Journal of Autism and Developmental Disorders*,
6103 *32*(4), 249–261. https://doi.org/10.1023/A:1016374617369

6104 Peretz, B., & Gluck, G. (1999). Assessing an active distracting technique for local anesthetic
6105 injection in pediatric dental patients: repeated deep breathing and blowing out air. *The*
6106 *Journal of Clinical Paediatric Dentistry*, *24*(1), 5–8.

6107 Peters, M. L. (2015). Emotional and Cognitive Influences on Pain Experience. In *Modern*
6108 *Trends in Pharmacopsychiatry*, *30*, 138–152. https://doi.org/10.1159/000435938

6109 Petersen-Felix, S., & Arendt-Nielsen, L. (2002). From pain research to pain treatment: The
6110 role of human experimental pain models. *Best Practice and Research: Clinical*
6111 *Anaesthesiology*, *16*(4), 667–680. https://doi.org/10.1053/bean.2002.0258

6112 Peterson, R. A., & Heilbronner, R. L. (1987). The anxiety sensitivity index:. Construct
6113 validity and factor analytic structure. *Journal of Anxiety Disorders*, *1*(2), 117–121.
6114 https://doi.org/10.1016/0887-6185(87)90002-8

6115 Pincus, T., & Morley, S. (2001). Cognitive-processing bias in chronic pain: A review and
6116 integration. In *Psychological Bulletin*, 127(5), 599–617. American Psychological
6117 Association Inc. https://doi.org/10.1037/0033-2909.127.5.599

6118 Pirker, W., & Katzenschlager, R. (2017). Gait disorders in adults and the elderly: A clinical
6119 guide. In *Wiener Klinische Wochenschrift*, *129*(3–4), 81–95.
6120 https://doi.org/10.1007/s00508-016-1096-4

6121 Pisula, E., & Ziegart-Sadowska, K. (2015). Broader autism phenotype in siblings of children
6122 with asd—a review. In *International Journal of Molecular Sciences*, *16*(6), 13217–
6123 13258. https://doi.org/10.3390/ijms160613217

6124 Poleshuck, E. L., & Green, C. R. (2008). Socioeconomic disadvantage and pain. *Pain*,
6125 136(3), 235–238. https://doi.org/10.1016/j.pain.2008.04.003

6126 Price, D. D., Milling, L. S., Kirsch, I., Duff, A., Montgomery, G. H., & Nicholls, S. S.
6127 (1999). An analysis of factors that contribute to the magnitude of placebo analgesia in an
6128 experimental paradigm. *Pain*, *83*(2), 147–156. https://doi.org/10.1016/S0304-
6129 3959(99)00081-0

6130 Prinzie, P., & Onghena, P. (2014). Cohort Sequential Design. In *Wiley StatsRef: Statistics*
6131 *Reference Online*. John Wiley & Sons, Ltd.
6132 https://doi.org/10.1002/9781118445112.stat06689

6133 Prkachin, K. M. (1992). The consistency of facial expressions of pain: a comparison across
6134 modalities. *Pain*, *51*(3), 297–306. https://doi.org/10.1016/0304-3959(92)90213-U

6135 Prkachin, K. M. (2009). Assessing pain by facial expression: facial expression as nexus. *Pain*
6136 *Research & Management*, *14*(1), 53–58. https://doi.org/10.1155/2009/542964

6137 Prkachin, K. M., & Mercer, S. R. (1989). Pain expression in patients with shoulder
6138 pathology: validity, properties and relationship to sickness impact. *Pain*, *39*(3), 257–
6139 265. https://doi.org/10.1016/0304-3959(89)90038-9

6140 Quartana, P. J., Campbell, C. M., & Edwards, R. R. (2009). Pain catastrophizing: a critical
6141 review. *Expert Review of Neurotherapeutics*, *9*(5), 745–758.
6142 https://doi.org/10.1586/ern.09.34

6143 Rainville, P., Bao, Q. V. H., & Chrétien, P. (2005). Pain-related emotions modulate
6144 experimental pain perception and autonomic responses. *Pain*, *118*(3), 306–318.
6145 https://doi.org/10.1016/j.pain.2005.08.022

6146 Rattaz, C., Dubois, A., Michelon, C., Viellard, M., Poinso, F., & Baghdadli, A. (2013). How
6147 do children with autism spectrum disorders express pain? A comparison with
6148 developmentally delayed and typically developing children. *Pain*, *154*(10), 2007–2013.
6149 https://doi.org/10.1016/j.pain.2013.06.011

6150 Read, J. C. A. (2015). The place of human psychophysics in modern neuroscience.
6151 *Neuroscience*, *296*, 116–129. https://doi.org/10.1016/j.neuroscience.2014.05.036

6152 Reynolds, S., & Lane, S. J. (2008). Diagnostic Validity of Sensory Over-Responsivity: A
6153 Review of the Literature and Case Reports. *Journal of Autism and Developmental*
6154 *Disorders*, *38*(3), 516–529. https://doi.org/10.1007/s10803-007-0418-9

6155 Rhudy, J. L., & Meagher, M. W. (2000). Fear and anxiety: divergent effects on human pain
6156 thresholds. *Pain*, *84*(1), 65–75. https://doi.org/10.1016/S0304-3959(99)00183-9

6157 Richards, C., Moss, J., Nelson, L., & Oliver, C. (2016). Persistence of self-injurious
6158 behaviour in autism spectrum disorder over 3 years: A prospective cohort study of risk
6159 markers. *Journal of Neurodevelopmental Disorders*, *8*(1), 21.
6160 https://doi.org/10.1186/s11689-016-9153-x

6161 Rickard, K. (1988). The occurrence of maladaptive health-related behaviors and teacher-rated

conduct problems in children of chronic low back pain patients. *Journal of Behavioral Medicine 1988 11:2*, *11*(2), 107–116. https://doi.org/10.1007/BF00848259

Ricky, C., Siobhan, O., Nawaf, M., & M., G. E. (2017). Factors associated with delayed diagnosis of mood and/oranxiety disorders. *Health Promotion and Chronic Disease Prevention in Canada : Research, Policy and Practice*, *37*(5), 137. https://doi.org/10.24095/HPCDP.37.5.02

Riddell, R. P., Flora, D. B., Stevens, S. A., Stevens, B., Cohen, L. L., Greenberg, S., & Garfield, H. (2013). Variability in infant acute pain responding meaningfully obscured by averaging pain responses. *Pain*, *154*(5), 714–721. https://doi.org/10.1016/j.pain.2013.01.015

Riquelme, I., Hatem, S. M., & Montoya, P. (2016). Abnormal Pressure Pain, Touch Sensitivity, Proprioception, and Manual Dexterity in Children with Autism Spectrum Disorders. *Neural Plasticity*, *2016*. https://doi.org/10.1155/2016/1723401

Robbins, B. D., & Vandree, K. (2009). The self-regulation of humor expression: A mixed method, phenomenological investigation of suppressed laughter. *Humanistic Psychologist*, *37*(1), 49–78. https://doi.org/10.1080/08873260802394533

Roberts, M. H., Klatzkin, R. R., & Mechlin, B. (2015). Social Support Attenuates Physiological Stress Responses and Experimental Pain Sensitivity to Cold Pressor Pain. *Annals of Behavioral Medicine*, *49*(4), 557–569. https://doi.org/10.1007/s12160-015-9686-3

Robertson, A. E., & Simmons, D. R. (2013). The relationship between sensory sensitivity and autistic traits in the general population. *Journal of Autism and Developmental Disorders*, *43*(4), 775–784. https://doi.org/10.1007/s10803-012-1608-7

Robertson, V. J. (Valma J. ., & Low, J. (John L.). (2006). *Electrotherapy explained : principles and practice*. Butterworth-Heinemann Elsevier.

Robinson, M. E., Bialosky, J. E., Bishop, M. D., Price, D. D., & George, S. Z. (2010). Supra-threshold scaling, temporal summation, and after-sensation: relationships to each other and anxiety/fear. In *Journal of Pain Research*. https://www.dovepress.com/

Roelofs, J., Peters, M. L., Deutz, J., Spijker, C., & Vlaeyen, J. W. S. (2005). The Fear of Pain Questionnaire (FPQ): Further psychometric examination in a non-clinical sample. *Pain*, *116*(3), 339–346. https://doi.org/10.1016/j.pain.2005.05.003

Rogers, S. J., Hepburn, S., & Wehner, E. (2003). Parent Reports of Sensory Symptoms in Toddlers with Autism and Those with Other Developmental Disorders. *Journal of Autism and Developmental Disorders*, *33*(6), 631–642. https://doi.org/10.1023/B:JADD.0000006000.38991.a7

Rolke, R., Baron, R., Maier, C., Tölle, T. R., Treede, R.-D., Beyer, A., Binder, A., Birbaumer, N., Birklein, F., Bötefür, I. C., Braune, S., Flor, H., Huge, V., Klug, R., Landwehrmeyer, G. B., Magerl, W., Maihöfner, C., Rolko, C., Schaub, C., … Wasserka, B. (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *PAIN*, *123*(3), 231–243. https://doi.org/10.1016/J.PAIN.2006.01.041

Rolke, R., Magerl, W., Campbell, K. A., Schalber, C., Caspari, S., Birklein, F., & Treede, R. D. (2006). Quantitative sensory testing: A comprehensive protocol for clinical trials. *European Journal of Pain*, *10*(1), 77. https://doi.org/10.1016/j.ejpain.2005.02.003

Rollman, G. B. (2005). The need for ecological validity in studies of pain and ethnicity. *Pain*, *113*(1), 3–4. https://doi.org/10.1016/j.pain.2004.10.015

6208 Rosen, T. E., Mazefsky, C. A., Vasa, R. A., & Lerner, M. D. (2018). Co-occurring
6209 psychiatric conditions in autism spectrum disorder.
6210 *Https://Doi.Org/10.1080/09540261.2018.1450229*, *30*(1), 40–61.
6211 https://doi.org/10.1080/09540261.2018.1450229

6212 Ross-Russell, M., & Sloan, P. (2005). Autoextraction in a child with autistic spectrum
6213 disorder. *British Dental Journal*, *198*(8), 473–474.
6214 https://doi.org/10.1038/sj.bdj.4812250

6215 Rothenberg, M. (n.d.). *The rebirth of Jonny | Harper's Magazine*. Retrieved September 8,
6216 2019, from https://harpers.org/archive/1960/02/the-rebirth-of-jonny/

6217 Rowbotham, S., Holler, J., Lloyd, D., & Wearden, A. (2012). How Do We Communicate
6218 About Pain? A Systematic Analysis of the Semantic Contribution of Co-speech Gestures
6219 in Pain-focused Conversations. *Journal of Nonverbal Behavior*, *36*(1), 1–21.
6220 https://doi.org/10.1007/s10919-011-0122-5

6221 Rutter, M. (2000). Genetic studies of autism: From the 1970s into the millennium. *Journal of*
6222 *Abnormal Child Psychology*, *28*(1), 3–14. https://doi.org/10.1023/A:1005113900068

6223 Ruzich, E., Allison, C., Smith, P., Watson, P., Auyeung, B., Ring, H., & Baron-Cohen, S.
6224 (2015). Measuring autistic traits in the general population: a systematic review of the
6225 Autism-Spectrum Quotient (AQ) in a nonclinical population sample of 6,900 typical
6226 adult males and females. *Molecular Autism*, *6*, 2. https://doi.org/10.1186/2040-2392-6-2

6227 Sacrey, L.-A. R., Zwaigenbaum, L., Bryson, S., Brian, J., Smith, I. M., Roberts, W.,
6228 Szatmari, P., Vaillancourt, T., Roncadin, C., & Garon, N. (2018). Parent and clinician
6229 agreement regarding early behavioral signs in 12- and 18-month-old infants at-risk of
6230 autism spectrum disorder. *Autism Research*, *11*(3), 539–547.

https://doi.org/10.1002/aur.1920

Salanti, G., & Ioannidis, J. P. A. (2009). Synthesis of observational studies should consider credibility ceilings. *Journal of Clinical Epidemiology*, *62*(2), 115–122. https://doi.org/10.1016/j.jclinepi.2008.05.014

Samwel, H. J. A., Evers, A. W. M., Crul, B. J. P., & Kraaimaat, F. W. (2006). The role of helplessness, fear of pain, and passive pain-coping in chronic pain patients. *Clinical Journal of Pain*, *22*(3), 245–251. https://doi.org/10.1097/01.AJP.0000173019.72365.F5

Saville, C. W. N., Shikhare, S., Iyengar, S., Daley, D., Intriligator, J., Boehm, S. G., Feige, B., & Klein, C. (2012). Is reaction time variability consistent across sensory modalities? Insights from latent variable analysis of single-trial P3b latencies. *Biological Psychology*, *91*(2), 275–282. https://doi.org/10.1016/J.BIOPSYCHO.2012.07.006

Saviola, F., Pappaianni, E., Monti, A., Grecucci, A., Jovicich, J., & De Pisapia, N. (2020). Trait and state anxiety are mapped differently in the human brain. *Scientific Reports*, *10*(1), 11112. https://doi.org/10.1038/s41598-020-68008-z

Schiavenato, M., & Craig, K. D. (2010). Pain Assessment as a Social Transaction. *The Clinical Journal of Pain*, *26*(8), 1. https://doi.org/10.1097/AJP.0b013e3181e72507

Schiefenhövel, W. (1995). Perception, Expression, and Social Function of Pain: A Human Ethological View. *Science in Context*, *8*(1), 31–46. https://doi.org/10.1017/S0269889700001885

Schiller, F. (1956). The cutaneous sensory modalities; a critique of their specificity. *A.M.A. Archives of Neurology and Psychiatry*, *75*(2), 203–219. http://www.ncbi.nlm.nih.gov/pubmed/13282539

6253 Schlereth, T., Magerl, W., & Treede, R. (2001). Spatial discrimination thresholds for pain and
6254 touch in human hairy skin. *Pain*, *92*(1–2), 187–194. https://doi.org/10.1016/s0304-
6255 3959(00)00484-x

6256 Schopler, E., & Reichler, R. J. (1972). How well do parents understand their own psychotic
6257 child? *Journal of Autism and Childhood Schizophrenia*, *2*(4), 387–400.
6258 https://doi.org/10.1007/BF01538171

6259 Schoth, D. E., Yu, K., & Liossi, C. (2014). The role of threat expectancy in attentional bias
6260 and thermal pain perception in healthy individuals. *Journal of Health Psychology*, *19*(5),
6261 653–663. https://doi.org/10.1177/1359105313476976

6262 Schott, G. D. (2004). Communicating the experience of pain: The role of analogy. *Pain*,
6263 *108*(3), 209–212. https://doi.org/10.1016/j.pain.2004.01.037

6264 Schrooten, M. G. S., Wiech, K., & Vlaeyen, J. W. S. (2014). When pain meets. Pain-related
6265 choice behavior and pain perception in different goal conflict situations. *Journal of Pain*,
6266 *15*(11), 1166–1178. https://doi.org/10.1016/j.jpain.2014.08.011

6267 Scott-Van Zeeland, A. A., Dapretto, M., Ghahremani, D. G., Poldrack, R. A., & Bookheimer,
6268 S. Y. (2010). Reward processing in autism. *Autism Research*, *3*(2), 53–67.
6269 https://doi.org/10.1002/aur.122

6270 Scott, R. C., & Tuchman, R. (2016). Epilepsy and autism spectrum disorders. *Neurology*,
6271 *87*(2), 130 LP – 131. https://doi.org/10.1212/WNL.0000000000002852

6272 Seymour, B., & Dolan, R. J. (2013). Emotion, Motivation, and Pain. In S. B. McMahon, M.
6273 Koltzenburg, & D. C. Tracey, I.Turk (Eds.), *Wall and Melzack's Textbook of Pain* (pp.
6274 248–255). Elsevier.

Shamay-Tsoory, S. G., & Mendelsohn, A. (2019). Real-Life Neuroscience: An Ecological Approach to Brain and Behavior Research. *Perspectives on Psychological Science*, *14*(5), 841–859. https://doi.org/10.1177/1745691619856350

Shaygan, M., Böger, A., & Kröner-Herwig, B. (2017). Valence and Arousal Value of Visual Stimuli and Their Role in the Mitigation of Chronic Pain: What Is the Power of Pictures? *Journal of Pain*, *18*(2), 124–131. https://doi.org/10.1016/j.jpain.2016.10.007

Sheldrick, R. C., Schlichting, L. E., Berger, B., Clyne, A., Ni, P., Perrin, E. C., & Vivier, P. M. (2019). Establishing new norms for developmental milestones. *Pediatrics*, *144*(6). https://doi.org/10.1542/peds.2019-0374

Siao Tick Chong, P., & Cros, D. P. (2004). Technology Literature Review: Quantitative Sensory Testing. *Muscle Nerve*, *29*, 734–747. https://doi.org/10.1002/mus.20053

Simon, D., Craig, K. D., Gosselin, F., Belin, P., & Rainville, P. (2008). Recognition and discrimination of prototypical dynamic expressions of pain and emotions. *Pain*, *135*(1–2), 55–64. https://doi.org/10.1016/j.pain.2007.05.008

Simons, S. H. P., & Tibboel, D. (2006). Pain perception development and maturation. *Seminars in Fetal and Neonatal Medicine*, *11*(4), 227–231. https://doi.org/10.1016/j.siny.2006.02.010

Smoski, M. J., & Bachorowski, J. A. (2003). Antiphonal laughter between friends and strangers. *Cognition and Emotion*, 17(2), 327–340. https://doi.org/10.1080/02699930302296

South, M., & Rodgers, J. (2017). Sensory, emotional and cognitive contributions to anxiety in autism spectrum disorders. *Frontiers in Human Neuroscience*, *11*(January), 1–7.

https://doi.org/10.3389/fnhum.2017.00020

Spezio, M. L., Adolphs, R., Hurley, R. S. E., & Piven, J. (2007a). Analysis of face gaze in autism using “Bubbles.” *Neuropsychologia*, *45*(1), 144–151. https://doi.org/10.1016/j.neuropsychologia.2006.04.027

Spezio, M. L., Adolphs, R., Hurley, R. S. E., & Piven, J. (2007b). Abnormal use of facial information in high-functioning autism. *Journal of Autism and Developmental Disorders*, *37*(5), 929–939. https://doi.org/10.1007/s10803-006-0232-9

Spinhoven, P., Ter Kuile, M., Kole-Snijders, A. M. J., Hutten Mansfeld, M., Den Ouden, D. J., & Vlaeyen, J. W. S. (2004). Catastrophizing and internal pain control as mediators of outcome in the multidisciplinary treatment of chronic low back pain. *European Journal of Pain*, *8*(3), 211–219. https://doi.org/10.1016/J.EJPAIN.2003.08.003

Spratt, E. G., Nicholas, J. S., Brady, K. T., Carpenter, L. A., Hatcher, C. R., Meekins, K. A., Furlanetto, R. W., & Charles, J. M. (2012). Enhanced cortisol response to stress in children in autism. *Journal of Autism and Developmental Disorders*, *42*(1), 75–81. https://doi.org/10.1007/s10803-011-1214-0

St. John Smith, E. (2017). Advances in understanding nociception and neuropathic pain. *Journal of Neurology 2017 265:2*, *265*(2), 231–238. https://doi.org/10.1007/S00415-017-8641-6

Stabel, A., Kroeger-Geoppinger, K., McCullagh, J., Weiss, D., McCullagh, J., Schneider, N., Newman, D. B., Schultz-Krohn, W., Volkmar, F. R., Glennon, T. J., Austin, S., Winterling, V., Spencer, E., Califano, C., Hansen, R., El-Fishawy, P., Scahill, L. D., Shtayermman, O., Benson, B. A., … Califano, C. (2013). Developmental Delay. In *Encyclopedia of Autism Spectrum Disorders* (pp. 887–888). Springer New York.

https://doi.org/10.1007/978-1-4419-1698-3_1427

Stanford, E. A., Chambers, C. T., & Craig, K. D. (2005). A normative analysis of the development of pain-related vocabulary in children. *Pain*, *114*(1–2), 278–284. https://doi.org/10.1016/j.pain.2004.12.029

Stawski, R. S., MacDonald, S. W. S., Brewster, P. W. H., Munoz, E., Cerino, E. S., & Halliday, D. W. R. (2019). A Comprehensive Comparison of Quantifications of Intraindividual Variability in Response Times: A Measurement Burst Approach. *The Journals of Gerontology: Series B*, *74*(3), 397–408. https://doi.org/10.1093/GERONB/GBX115

Stephens, R., Atkins, J., & Kingston, A. (2009). Swearing as a response to pain. *Neuroreport*, *20*(12), 1056–1060. https://doi.org/10.1097/WNR.0B013E32832E64B1

Stephens, R., & Umland, C. (2011). Swearing as a response to pain-effect of daily swearing frequency. *The Journal of Pain*, *12*(12), 1274–1281. https://doi.org/10.1016/J.JPAIN.2011.09.004

Stewart, M. E., & Austin, E. J. (2009). The structure of the Autism-Spectrum Quotient (AQ): Evidence from a student sample in Scotland. *Personality and Individual Differences*, *47*(3), 224–228. https://doi.org/10.1016/j.paid.2009.03.004

Stochl, J., Whittier, A., Wagner, A. P., Veijola, J., Jääskeläinen, E., Miettunen, J., Khandaker, G. M., & Jones, P. B. (2019). Association between developmental milestones and age of schizophrenia onset: Results from the Northern Finland Birth Cohort 1966. *Schizophrenia Research*, *208*, 228–234. https://doi.org/10.1016/j.schres.2019.02.013

Stoel-Gammon, C. (2011). Relationships between lexical and phonological development in

young children*. *Journal of Child Language*, *38*(1), 1–34. https://doi.org/10.1017/S0305000910000425

Strulov, L., Zimmer, E. Z., Granot, M., Tamir, A., Jakobi, P., & Lowenstein, L. (2007). Pain Catastrophizing, Response to Experimental Heat Stimuli, and Post-Cesarean Section Pain. *Journal of Pain*, *8*(3), 273–279. https://doi.org/10.1016/j.jpain.2006.09.004

Sucksmith, E., Roth, I., & Hoekstra, R. A. (2011). Autistic traits below the clinical threshold: Re-examining the broader autism phenotype in the 21st century. *Neuropsychology Review*, *21*(4), 360–389. https://doi.org/10.1007/s11065-011-9183-9

Sullivan, M. D. (1995). Pain in language. *Pain Forum*, *4*(1), 3–14. https://doi.org/10.1016/S1082-3174(11)80068-1

Sullivan, M. J. L., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and Validation. *Psychological Assessment*, *7*(4), 524–532. https://doi.org/10.1037/1040-3590.7.4.524

Sullivan, M. J. L., Thorn, B., Haythornthwaite, J. A., Keefe, F., Martin, M., Bradley, L. A., & Lefebvre, J. C. (2001). Theoretical perspectives on the relation between catastrophizing and pain. *Clinical Journal of Pain*, *17*(1), 52–64. https://doi.org/10.1097/00002508-200103000-00008

Swee, G., & Schirmer, A. (2015). On the Importance of Being Vocal: Saying "Ow" Improves Pain Tolerance. *The Journal of Pain*, *16*(4), 326–334. https://doi.org/10.1016/J.JPAIN.2015.01.002

Swinkels-Meewisse, E. J. C. M., Swinkels, R. A. H. M., Verbeek, A. L. M., Vlaeyen, J. W. S., & Oostendorp, R. A. B. (2003). Psychometric properties of the Tampa Scale for

6364 kinesiophobia and the fear-avoidance beliefs questionnaire in acute low back pain.
6365 *Manual Therapy*, *8*(1), 29–36. https://doi.org/10.1054/math.2002.0484

6366 Szatmari, P., Archer, L., Fisman, S., Streiner, D. L., & Wilson, F. (1995). Asperger's
6367 Syndrome and Autism: Differences in Behavior, Cognition, and Adaptive Functioning.
6368 *Journal of the American Academy of Child and Adolescent Psychiatry*, *34*(12), 1662–
6369 1671. https://doi.org/10.1097/00004583-199512000-00017

6370 Tager-Flusberg, H. (1999). A psychological approach to understanding the social and
6371 language impairments in autism. In *International Review of Psychiatry* (Vol. 11, Issue 4,
6372 pp. 325–334). Taylor & Francis. https://doi.org/10.1080/09540269974203

6373 Taghizadeh, N., Davidson, A., Williams, K., & Story, D. (2015). Autism spectrum disorder
6374 (ASD) and its perioperative management. *Pediatric Anesthesia*, *25*(11), 1076–1084.
6375 https://doi.org/10.1111/pan.12732

6376 Tang, J., & Gibson, S. J. (2005). A psychophysical evaluation of the relationship between
6377 trait anxiety, pain perception, and induced state anxiety. *Journal of Pain*, *6*(9), 612–619.
6378 https://doi.org/10.1016/j.jpain.2005.03.009

6379 Tavassoli, T., Hoekstra, R. A., & Baron-Cohen, S. (2014). The Sensory Perception Quotient
6380 (SPQ): Development and validation of a new sensory questionnaire for adults with and
6381 without autism. *Molecular Autism*, *5*(1), 1–10. https://doi.org/10.1186/2040-2392-5-29

6382 Telzer, E. H., McCormick, E. M., Peters, S., Cosme, D., Pfeifer, J. H., & van Duijvenvoorde,
6383 A. C. K. (2018). Methodological considerations for developmental longitudinal fMRI
6384 research. *Developmental Cognitive Neuroscience*, *33*, 149–160.
6385 https://doi.org/10.1016/j.dcn.2018.02.004

6386 Thibodeau, M. A., Welch, P. G., Katz, J., & Asmundson, G. J. G. (2013). Pain-related
6387 anxiety influences pain perception differently in men and women: A quantitative
6388 sensory test across thermal pain modalities. *Pain*, *154*(3), 419–426.
6389 https://doi.org/10.1016/j.pain.2012.12.001

6390 Thomas, S., Hovinga, M. E., Rai, D., & Lee, B. K. (2017). Brief Report: Prevalence of Co-
6391 occurring Epilepsy and Autism Spectrum Disorder: The U.S. National Survey of
6392 Children's Health 2011--2012. *Journal of Autism and Developmental Disorders*, *47*(1),
6393 224–229. https://doi.org/10.1007/s10803-016-2938-7

6394 Thompson, T., Correll, C. U., Gallop, K., Vancampfort, D., & Stubbs, B. (2016). Is Pain
6395 Perception Altered in People With Depression? A Systematic Review and Meta-
6396 Analysis of Experimental Pain Research. *The Journal of Pain*, *17*(12), 1257–1272.
6397 https://doi.org/10.1016/j.jpain.2016.08.007

6398 Tomchek, S. D., & Dunn, W. (2007). Sensory Processing in Children With and Without
6399 Autism: A Comparative Study Using the Short Sensory Profile. *American Journal of*
6400 *Occupational Therapy*, *61*(2), 190–200. https://doi.org/10.5014/ajot.61.2.190

6401 Tordjman, S., Anderson, G. M., Botbol, M., Brailly-Tabard, S., Perez-Diaz, F., Graignic, R.,
6402 Carlier, M., Schmit, G., Rolland, A. C., Bonnot, O., Trabado, S., Roubertoux, P., &
6403 Bronsard, G. (2009). Pain reactivity and plasma β-endorphin in children and adolescents
6404 with autistic disorder. *PLoS ONE*, *4*(8). https://doi.org/10.1371/journal.pone.0005289

6405 Torrance, N., Smith, B. H., Bennett, M. I., & Lee, A. J. (2006). The Epidemiology of Chronic
6406 Pain of Predominantly Neuropathic Origin. Results From a General Population Survey.
6407 *Journal of Pain*, *7*(4), 281–289. https://doi.org/10.1016/j.jpain.2005.11.008

6408 Torta, D. M., Legrain, V., Mouraux, A., & Valentini, E. (2017). Attention to pain! A

6409 neurocognitive perspective on attentional modulation of pain in neuroimaging studies. In
6410 *Cortex*, *89*, 120–134. https://doi.org/10.1016/j.cortex.2017.01.010

6411 Tracey, I. (2010). Getting the pain you expect: mechanisms of placebo, nocebo and
6412 reappraisal effects in humans. *Nature Medicine*, *16*(11), 1277–1283.
6413 https://doi.org/10.1038/nm.2229

6414 Treede, R. D. (2006). Chapter 1 Pain and hyperalgesia: definitions and theories. *Handbook of*
6415 *Clinical Neurology*, *81*, 3–10. https://doi.org/10.1016/S0072-9752(06)80005-9

6416 Treede, R. D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers,
6417 S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Korwisi, B., Kosek,
6418 E., Lavand'Homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., … Wang, S. J.
6419 (2019). Chronic pain as a symptom or a disease: The IASP Classification of Chronic
6420 Pain for the International Classification of Diseases (ICD-11). *Pain*, *160*(1), 19–27.
6421 https://doi.org/10.1097/J.PAIN.0000000000001384

6422 Treutwein, B. (1995). Adaptive psychophysical procedures. *Vision Research*, *35*(17), 2503–
6423 2522. https://doi.org/10.1016/0042-6989(95)00016-X

6424 Trevisan, D. A., Hoskyn, M., & Birmingham, E. (2018). Facial Expression Production in
6425 Autism: A Meta-Analysis. *Autism Research*, *11*(12), 1586–1601.
6426 https://doi.org/10.1002/aur.2037

6427 Tursky, B., Jamner, L. D., & Friedman, R. (1982). The pain perception profile: A
6428 psychophysical approach to the assessment of pain report. *Behavior Therapy*, *13*(4),
6429 376–394. https://doi.org/10.1016/S0005-7894(82)80002-6

6430 Uddin, L. Q., Supekar, K., Lynch, C. J., Khouzam, A., Phillips, J., Feinstein, C., Ryali, S., &

Menon, V. (2013). Salience network-based classification and prediction of symptom severity in children with autism. *JAMA Psychiatry*, *70*(8), 869–879. https://doi.org/10.1001/jamapsychiatry.2013.104

Uhl, I., Krumova, E. K., Regeniter, S., Bar, K. J., Norra, C., Richter, H., Assion, H. J., Westermann, A., Juckel, G., & Maier, C. (2011). Association between wind-up ratio and central serotonergic function in healthy subjects and depressed patients. In *Neuroscience Letters*, *504*(2), 176–180. http://search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000297535000021&site=eds-live

Uljarević, M., Phillips, J. M., Schuck, R. K., Schapp, S., Solomon, E. M., Salzman, E., Allerhand, L., Libove, R. A., Frazier, T. W., & Hardan, A. Y. (2020). Exploring Social Subtypes in Autism Spectrum Disorder: A Preliminary Study. *Autism Research*, *13*(8), 1335–1342. https://doi.org/10.1002/aur.2294

Unruh, K. E., Sasson, N. J., Shafer, R. L., Whitten, A., Miller, S. J., Turner-Brown, L., & Bodfish, J. W. (2016). Social Orienting and Attention Is Influenced by the Presence of Competing Nonsocial Information in Adolescents with Autism. *Frontiers in Neuroscience*, *10*(DEC), 586. https://doi.org/10.3389/FNINS.2016.00586

Valderas, J. M., Starfield, B., Sibbald, B., Salisbury, C., & Roland, M. (2009). Defining comorbidity: implications for understanding health and health services. *Annals of Family Medicine*, *7*(4), 357–363. https://doi.org/10.1370/afm.983

Van Damme, S., Crombez, G., & Eccleston, C. (2008). Coping with pain: A motivational perspective. *Pain*, *139*(1), 1–4. https://doi.org/10.1016/j.pain.2008.07.022

Van Damme, S., Legrain, V., Vogt, J., & Crombez, G. (2010). Keeping pain in mind: A

motivational account of attention to pain. *Neuroscience and Biobehavioral Reviews*, *34*(2), 204–213. https://doi.org/10.1016/j.neubiorev.2009.01.005

Van Damme, S., & Moore, D. J. (2012). From the clinic to the lab (and back)—a call for laboratory research to optimize cognitive behavioural treatment of pain. *Translational Behavioral Medicine*, *2*(1), 102–105. https://doi.org/10.1007/s13142-011-0083-6

Van Damme, S., Van Ryckeghem, D. M. L., Wyffels, F., Van Hulle, L., & Crombez, G. (2012). No pain no gain? Pursuing a competing goal inhibits avoidance behavior. *Pain*, *153*(4). https://journals.lww.com/pain/Fulltext/2012/04000/No_pain_no_gain__Pursuing_a_competing_goal.13.aspx

van den Bosch, G. E., van Dijk, M., Tibboel, D., & Valkenburg, A. J. (2017). Thermal quantitative sensory testing in healthy Dutch children and adolescents standardized test paradigm and Dutch reference values. *BMC Pediatrics 2017 17:1*, *17*(1), 1–10. https://doi.org/10.1186/S12887-017-0827-7

van Steensel, F. J. A., & Heeman, E. J. (2017). Anxiety Levels in Children with Autism Spectrum Disorder: A Meta-Analysis. *Journal of Child and Family Studies*, *26*(7), 1753–1767. https://doi.org/10.1007/s10826-017-0687-7

Vance, M., & Wells, B. (1994). The wrong end of the stick: language-impaired children's understanding of non-literal language. *Child Language Teaching and Therapy*, *10*(1), 23–46. https://doi.org/10.1177/026565909401000102

Vandewalle, K., & Melia, Y. (2021). Psychosocial and behavioural factors associated with self injurious behaviour (SIB) in individuals with autism spectrum disorders (ASD). In *Research in Autism Spectrum Disorders*, *81*, 101713.

https://doi.org/10.1016/j.rasd.2020.101713

Vasa, R. A., & Mazurek, M. O. (2015). An update on anxiety in youth with autism spectrum disorders. *Current Opinion in Psychiatry*, *28*(2), 83. https://doi.org/10.1097/YCO.0000000000000133

Vaughan, S., Failla, M. D., Poole, H. M., Forshaw, M. J., McGlone, F., Cascio, C. J., & Moore, D. J. (2019). Pain Processing in Psychiatric Conditions: A Systematic Review. *Review of General Psychology*, *23*(3). https://doi.org/10.1177/1089268019842771

Vaughan, S., McGlone, F., Poole, H., & Moore, D. J. (2019). A Quantitative Sensory Testing Approach to Pain in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-019-03918-0

Vervoort, T., Caes, L., Trost, Z., Sullivan, M., Vangronsveld, K., & Goubert, L. (2011). Social modulation of facial pain display in high-catastrophizing children: An observational study in schoolchildren and their parents. *Pain*, *152*(7), 1591–1599. https://doi.org/10.1016/j.pain.2011.02.048

Victorio, M. (2014). Headaches in patients with autism spectrum disorder. *The Journal of Headache and Pain*, *15*(1), B37. https://doi.org/10.1186/1129-2377-15-S1-B37

Villemure, C., & Bushnell, M. C. (2002). Cognitive modulation of pain: How do attention and emotion influence pain processing? In *Pain* (Vol. 95, Issue 3, pp. 195–199). Pain. https://doi.org/10.1016/S0304-3959(02)00007-6

Vivanti, G., Hocking, D. R., Fanning, P. A. J., Uljarevic, M., Postorino, V., Mazzone, L., & Dissanayake, C. (2018). Attention to novelty versus repetition: Contrasting habituation profiles in Autism and Williams syndrome. *Developmental Cognitive Neuroscience*, *29*,

54–60. https://doi.org/10.1016/j.dcn.2017.01.006

Vlaeyen, J. W. S., Crombez, G., & Linton, S. J. (2016). The fear-avoidance model of pain. *Pain157*(8). https://journals.lww.com/pain/Fulltext/2016/08000/The_fear_avoidance_model_of_pain.5.aspx

Vlaeyen, J. W. S., Hanssen, M., Goubert, L., Vervoort, T., Peters, M., van Breukelen, G., Sullivan, M. J. L., & Morley, S. (2009). Threat of pain influences social context effects on verbal pain report and facial expression. *Behaviour Research and Therapy*, *47*(9), 774–782. https://doi.org/10.1016/j.brat.2009.05.008

Vlaeyen, J. W. S., & Linton, S. J. (2012). Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain*, *153*(6), 1144–1147. https://doi.org/10.1016/j.pain.2011.12.009

Volkmar, F. R., & Reichow, B. (2013a). Autism in DSM-5: progress and challenges. *Molecular Autism*, *4*(1), 13. https://doi.org/10.1186/2040-2392-4-13

von Baeyer, C. L., Piira, T., Chambers, C. T., Trapanotto, M., & Zeltzer, L. K. (2005). Guidelines for the cold pressor task as an experimental pain stimulus for use with children. *The Journal of Pain : Official Journal of the American Pain Society*, *6*(4), 218–227. https://doi.org/10.1016/j.jpain.2005.01.349

von Baeyer, C. L., & Spagrud, L. J. (2007). Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. *Pain*, *127*(1–2), 140–150. https://doi.org/10.1016/j.pain.2006.08.014

Voudouris, N. J., Peck, C. L., & Coleman, G. (1989). Conditioned response models of placebo phenomena: further support. *Pain*, *38*(1), 109–116.

https://doi.org/10.1016/0304-3959(89)90080-8

Walker, S. C., & McGlone, F. P. (2013). The social brain: Neurobiological basis of affiliative behaviours and psychological well-being. *Neuropeptides*, *47*(6), 379–393. https://doi.org/10.1016/J.NPEP.2013.10.008

Walsh, J., Eccleston, C., & Keogh, E. (2014). Pain communication through body posture: The development and validation of a stimulus set. *Pain*, *155*(11), 2282–2290. https://doi.org/10.1016/j.pain.2014.08.019

Wang, P. S., Berglund, P., Olfson, M., Pincus, H. A., Wells, K. B., & Kessler, R. C. (2005). Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 603–613. https://doi.org/10.1001/ARCHPSYC.62.6.603

Watson, A. B. (2017). QUEST+: A general multidimensional Bayesian adaptive psychometric method. *Journal of Vision*, *17*(3), 10–10. https://doi.org/10.1167/17.3.10

Werner, M. U., Petersen, M. A., & Bischoff, J. M. (2013). Test-retest studies in quantitative sensory testing: A critical review. *Acta Anaesthesiologica Scandinavica*, *57*(8), 957–963. https://doi.org/10.1111/aas.12150

Wheelwright, S., Auyeung, B., Allison, C., & Baron-Cohen, S. (2010). Defining the broader, medium and narrow autism phenotype among parents using the Autism Spectrum Quotient (AQ). *Molecular Autism*, *1*(1). https://doi.org/10.1186/2040-2392-1-10

Whitaker, C., Stevelink, S., & Fear, N. (2017). The use of Facebook in recruiting participants for health research purposes: A systematic review. In *Journal of Medical Internet Research* (Vol. 19, Issue 8, p. e290). JMIR Publications Inc.

https://doi.org/10.2196/jmir.7071

Whyatt, C., & Craig, C. (2013). Sensory-motor problems in Autism. *Frontiers in Integrative Neuroscience*, *0*(JUN), 51. https://doi.org/10.3389/FNINT.2013.00051

Wideman, T. H., Edwards, R. R., Walton, D. M., Martel, M. O., Hudon, A., & Seminowicz, D. A. (2019). The Multimodal Assessment Model of Pain. *Clinical Journal of Pain*, *35*(3), 212–221. https://doi.org/10.1097/AJP.0000000000000670

Wieckowski, A. T., & White, S. W. (2017a). Eye-Gaze Analysis of Facial Emotion Recognition and Expression in Adolescents with ASD. *Journal of Clinical Child and Adolescent Psychology*, *46*(1), 110–124. https://doi.org/10.1080/15374416.2016.1204924

Wieckowski, A. T., & White, S. W. (2017b). Eye-Gaze Analysis of Facial Emotion Recognition and Expression in Adolescents with ASD. *Journal of Clinical Child and Adolescent Psychology*, *46*(1), 110–124. https://doi.org/10.1080/15374416.2016.1204924

Wiggins, L. D., Tian, L. H., Levy, S. E., Rice, C., Lee, L. C., Schieve, L., Pandey, J., Daniels, J., Blaskey, L., Hepburn, S., Landa, R., Edmondson-Pretzel, R., & Thompson, W. (2017). Homogeneous Subgroups of Young Children with Autism Improve Phenotypic Characterization in the Study to Explore Early Development. *Journal of Autism and Developmental Disorders*, *47*(11), 3634–3645. https://doi.org/10.1007/s10803-017-3280-4

Wigham, S., Rodgers, J., South, M., McConachie, H., & Freeston, M. (2015). The Interplay Between Sensory Processing Abnormalities, Intolerance of Uncertainty, Anxiety and Restricted and Repetitive Behaviours in Autism Spectrum Disorder. *Journal of Autism*

and Developmental Disorders, *45*(4), 943–952. https://doi.org/10.1007/s10803-014-2248-x

Wilbarger, J. L., McIntosh, D. N., & Winkielman, P. (2009). Startle modulation in autism: Positive affective stimuli enhance startle response. *Neuropsychologia*, *47*(5), 1323–1331. https://doi.org/https://doi.org/10.1016/j.neuropsychologia.2009.01.025

Williams, A. C. D. C., & Craig, K. D. (2016). Updating the definition of pain. *Pain*, *157*(11), 2420–2423. https://doi.org/10.1097/j.pain.0000000000000613

Williams, D. (1999). *Somebody somewhere : breaking free from the world of autism*. Jessica Kingsley Publishers.

Williams, Z. J., Failla, M. D., Davis, S. L., Heflin, B. H., Okitondo, C. D., Moore, D. J., & Cascio, C. J. (2019a). Thermal Perceptual Thresholds are typical in Autism Spectrum Disorder but Strongly Related to Intra- individual Response Variability. *Scientific Reports*, *March*, 1–14. https://doi.org/10.1038/s41598-019-49103-2

Willis, W. D., & Coggeshall, R. E. (2004). Introduction. *Sensory Mechanisms of the Spinal Cord*, 1–17. https://doi.org/10.1007/978-1-4615-0035-3_1

Wing, J. K. (John K. (1976). *Early childhood autism; clinical, educational and social aspects.* Pergamon Press.

Wing, L. (1966). Autistic Children: A Guide for Parents and Professionals. *The British Journal of Psychiatry*, *112*(483), 211–212. https://doi.org/10.1192/bjp.112.483.211-a

Wong, D. L., & Baker, C. M. (2001). Smiling face as anchor for pain intensity scales. *Pain*, *89*(2), 295–297. https://doi.org/10.1016/S0304-3959(00)00375-4

6587 Woodforde, J. M., & Merskey, H. (1972). Some relationships between subjective measures of
6588 pain. *Journal of Psychosomatic Research*, *16*(3), 173–178. https://doi.org/10.1016/0022-
6589 3999(72)90041-4

6590 Wright, D. B., & London, K. (2009). Multilevel modelling: Beyond the basic applications.
6591 *British Journal of Mathematical and Statistical Psychology*, *62*(2), 439–456.
6592 https://doi.org/10.1348/000711008X327632

6593 Yamada, M., & Decety, J. (2009). Unconscious affective processing and empathy: An
6594 investigation of subliminal priming on the detection of painful facial expressions. *Pain*,
6595 *143*, 71–75.

6596 Yarnitsky, D., Bouhassira, D., Drewes, A. M., Fillingim, R. B., Granot, M., Hansson, P.,
6597 Landau, R., Marchand, S., Matre, D., Nilsen, K. B., Stubhaug, A., Treede, R. D., &
6598 Wilder-Smith, O. H. G. (2015). Recommendations on practice of conditioned pain
6599 modulation (CPM) testing. *European Journal of Pain*, *19*(6), 805–806.
6600 https://doi.org/10.1002/ejp.605

6601 Yasuda, Y., Hashimoto, R., Nakae, A., Kang, H., Ohi, K., Yamamori, H., Fujimoto, M.,
6602 Hagihira, S., & Takeda, M. (2016). Sensory cognitive abnormalities of pain in autism
6603 spectrum disorder: A case-control study. *Annals of General Psychiatry*, *15*(1).
6604 https://doi.org/10.1186/s12991-016-0095-1

6605 Yates, T. M. (2004). The developmental psychopathology of self-injurious behavior:
6606 Compensatory regulation in posttraumatic adaptation. *Clinical Psychology Review*,
6607 *24*(1), 35–74. https://doi.org/10.1016/J.CPR.2003.10.001

6608 Yirmiya, N., Kasari, C., Sigman, M., & Mundy, P. (1989). Facial Expressions of Affect in
6609 Autistic, Mentally Retarded and Normal Children. *Journal of Child Psychology and*

Psychiatry, *30*(5), 725–735. https://doi.org/10.1111/j.1469-7610.1989.tb00785.x

Yoshimura, S., Sato, W., Uono, S., & Toichi, M. (2015). Impaired Overt Facial Mimicry in Response to Dynamic Facial Expressions in High-Functioning Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*, *45*(5), 1318–1328. https://doi.org/10.1007/s10803-014-2291-7

Young, G. B., & Blume, W. T. (1983). Painful Epileptic Seizures. *Brain*, *106*(3), 537–554. https://doi.org/10.1093/brain/106.3.537

Younger, J., Aron, A., Parke, S., Chatterjee, N., & Mackey, S. (2010). Viewing Pictures of a Romantic Partner Reduces Experimental Pain: Involvement of Neural Reward Systems. *PLoS ONE*, *5*(10), e13309. https://doi.org/10.1371/journal.pone.0013309

Zaccagnino, M. P., & Nedeljkovic, S. S. (2017). Pain assessment tools. In *Pain Medicine: An Essential Review* (pp. 77–81). Springer International Publishing. https://doi.org/10.1007/978-3-319-43133-8_21

Zaman, J., Wiech, K., Claes, N., Van Oudenhove, L., Van Diest, I., & Vlaeyen, J. W. S. (2018). The Influence of Pain-Related Expectations on Intensity Perception of Nonpainful Somatosensory Stimuli. *Psychosomatic Medicine*, *80*(9), 836–844. https://doi.org/10.1097/PSY.0000000000000586

Zane, E., Neumeyer, K., Mertens, J., Chugg, A., & Grossman, R. B. (2018). I Think We're Alone Now: Solitary Social Behaviors in Adolescents with Autism Spectrum Disorder. *Journal of Abnormal Child Psychology*, *46*(5), 1111–1120. https://doi.org/10.1007/s10802-017-0351-0

Zhou, X., Vohs, K. D., & Baumeister, R. F. (2009). The symbolic power of money:

Reminders of money alter social distress and physical pain. *Psychological Science*, *20*(6), 700–706. https://doi.org/10.1111/j.1467-9280.2009.02353.x

Zwick, G. P. (2017). Neuropsychological assessment in autism spectrum disorder and related conditions. *Dialogues in Clinical Neuroscience*, *19*(4), 373–379. https://doi.org/10.31887/dcns.2017.19.4/gzwick

Appendix A. Published Paper of Chapter 2 Experiment 2

Journal of Autism and Developmental Disorders (2020) 50:1607–1620
https://doi.org/10.1007/s10803-019-03918-0

ORIGINAL PAPER

A Quantitative Sensory Testing Approach to Pain in Autism Spectrum Disorders

Sarah Vaughan[1,2] · Francis McGlone[1,3] · Helen Poole[1] · David J. Moore[1,4]

Published online: 15 February 2019

Abstract
Sensory abnormalities in autism has been noted clinically, with pain insensitivity as a specified diagnostic criterion. However, there is limited research using psychophysically robust techniques. Thirteen adults with ASD and 13 matched controls completed an established quantitative sensory testing (QST) battery, supplemented with measures of pain tolerance and central modulation. The ASD group showed higher thresholds for light touch detection and mechanical pain. Notably, the ASD group had a greater range of extreme scores (the number of z-scores outside of the 95% CI > 2), dynamic mechanical allodynia and paradoxical heat sensation; phenomena not typically seen in neurotypical individuals. These data support the need for research examining central mechanisms for pain in ASD and greater consideration of individual difference.

Keywords Autism · Quantitative sensory testing · Pain · Somatosensation

Introduction

In addition to the most striking lifelong effects of impaired communication, socialization and restrictive/repetitive behaviours in autism spectrum disorder (ASD), there is a high prevalence of sensory perceptual anomalies (Baranek 2002). Evidence for which has relied on autobiographical, observational or behavioural measures (Moore 2015) which has demonstrated, amongst an array of sensory disturbances, an absence of typical pain behaviours (e.g. absence of hand withdrawal reflex or a lack of protective body positioning) when encountering pain (Bursch et al. 2004; Gillberg and Coleman 2000; Mahler 1952; Rothenberg 1960; Wing 1996). There is further evidence that autistic individuals have aversions to touch (Grandin 1992, 1995; Williams 2015), suggesting that light tactile sensation might be a source of discomfort, indicating a potential hypersensitivity to tactile stimuli (Kaiser et al. 2016; Moore 2015). However, such methods are typically not generalizable because it is unclear whether the case investigated is representative of the wider body of "similar" instances. Further validation of this phenomenon is given by the re-incorporation of sensory responses as a feature in diagnostic texts suggesting that it is a central clinical finding in autism (APA 2013). There is however, a dearth of rigorous psychophysical experimental evidence to support these claims. Therefore, the current study aims to clarify the characteristics of *pain* sensitivity associated with ASD using a psychophysically robust experimental case-control design.

Pain is multifaceted, defined as a distressing experience associated with actual or potential tissue damage; with sensory, emotional, cognitive and social components (IASP 2012; Williams and Craig 2016). Together, the percept, and the subjective reaction act as a warning system so that individuals learn to avoid dangerous stimuli (Yasuda et al. 2016), whilst also promoting behavioural analgesia (Eccleston and Crombez 1999). A disruption to this system could result in a lack of these learned behaviours.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10803-019-03918-0) contains supplementary material, which is available to authorized users.

✉ David J. Moore
D.J.Moore@ljmu.ac.uk

[1] School of Natural Sciences and Psychology, Psychology Department, Liverpool John Moores University, Liverpool L3 3AF, UK

[2] Faculty of Social Sciences, School of Psychology, Chester University, Chester CH1 4BJ, UK

[3] Institute of Psychology, Health and Society, University of Liverpool, Liverpool L69 3GL, UK

[4] Department of Natural Sciences and Psychology, Liverpool John Moores University, Liverpool L3 3AF, UK

Article

Review of General Psychology
2019, Vol. 23(3) 336–358
© American Psychological Association 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1089268019842771
journals.sagepub.com/home/rgp
SAGE

Pain Processing in Psychiatric Conditions: A Systematic Review

Sarah Vaughan[1,2], Michelle D. Failla[3], Helen M. Poole[1], Mark J. Forshaw[1], Francis McGlone[1], Carissa J. Cascio[3], and David J. Moore[1]

Abstract

Pain is a universal, multidimensional experience with sensory, emotional, cognitive, and social components, which is fundamental to our environmental learning when functioning typically. Understanding pain processing in psychiatric conditions could provide unique insight into the underlying pathophysiology or psychiatric disease, especially given the psychobiological overlap with pain processing pathways. Studying pain in psychiatric conditions is likely to provide important insights, yet, there is a limited understanding beyond the work in depression and anxiety. This is a missed opportunity to describe psychiatric conditions in terms of neurobiological alterations. To examine the research into the pain experiences of these groups and the extent to which a-typicality is present, a systematic review was conducted. An electronic search strategy was developed and conducted in several databases. The current systematic review included 46 studies covering five *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*) disorders: autism, attention-deficit hyperactivity disorder (ADHD), schizophrenia, personality disorder, and eating disorders, confirming tentative evidence of altered pain and touch processing. Specifically, hyposensitivity is reported in schizophrenia, personality disorder and eating disorder, hypersensitivity in ADHD, and mixed results for autism. Review of the research highlights a degree of methodological inconsistency in the utilization of comprehensive protocols, the lack of which fails to allow us to understand whether a-typicality is systemic or modality specific.

Keywords

psychiatric, *DSM-5*, pain, quantitative sensory testing, QST

Introduction

Pain is a universal, multidimensional experience with sensory, emotional, cognitive, and social components (Williams & Craig, 2016). Understanding pain processing in psychiatric conditions could provide unique insight into the underlying pathophysiology or psychiatric disease, especially given the psychobiological overlap with pain processing pathways (Bird et al., 2010; de la Fuente-Sandoval, Favila, Gómez-Martin, Pellicer, & Graff-Guerrero, 2010; Fan, Chen, Chen, Decety, & Cheng, 2014; Goesling, Clauw, & Hassett, 2013; Iannetti & Mouraux, 2010). For example, there is substantial literature on pain perception in anxiety and depression (for review, see Thompson, Correll, Gallop, Vancampfort, & Stubbs, 2016) supporting a bidirectional relationship between these conditions and altered pain behaviors. From this literature, several examples have emerged that highlight the need to understand pain perception in psychiatric disorders. The co-occurrence of depression or anxiety and pain has an additive burden on the individual (Bair, Robinson, Katon, & Kroenke, 2003). Similarly, altered pain behaviors can lead individuals to look for somatic causes, potentially obscuring or delaying psychiatric diagnoses. There also seems to be important moderators between depression/anxiety and pain, specifically related to the exteroceptive or interoceptive nature of the stimuli and attentional resources allocated for painful stimuli, which provide insight into sensory processing in the disorder (Goesling et al., 2013; Thompson et al., 2016).

Studying pain in psychiatric conditions is likely to provide important insights, yet, there is a limited understanding beyond the work outside depression and anxiety. This is a

[1]Liverpool John Moores University, Liverpool, UK
[2]University of Chester, Chester, UK
[3]Vanderbilt University Medical Center, Nashville, TN, USA

Corresponding Author:
David J. Moore, Psychology Department, School of Natural Sciences and Psychology, Liverpool John Moores University, Liverpool L3 3AF, UK.
Email: D.J.Moore@ljmu.ac.uk

6641

Appendix C. Quantitative Sensory Testing Script

Thermal detection and pain thresholds

"During this procedure, the thermal stimulator will be used to deliver cold temperature. We are primarily interested in the sensation you experience as the temperature decreases. We would like you to tell us when you first experience the cold sensation as a result of the procedure. As soon as the device first produces a sensation, let us know – please say signal with your opposite hand. Do you have any questions?"

This will then be repeated for warm sensation.

"During this procedure, the thermal stimulator will be used to deliver warm stimulation. We are primarily interested in the pain you experience as the temperature increases. We would like you to tell us when you first feel pain as a result of the procedure. As soon as the device first produces a pain sensation, let us know – please say "pain" or signal with your hand. Do you have any questions?"

This will then be repeated for cold pain.

Tactile Detection Threshold

"This is to test your ability to detect light touch. I will touch your skin with a Von Frey Hair and if you can tell me "yes" as soon as you perceive a sensation on your hand"

Mechanical Pain Threshold

"During this procedure, I will touch your skin once with the weighted pinprick. Please indicate when the feeling becomes sharp or stinging. We will then redo the test and this time can you tell us when the sensation becomes blunt and not painful".

Mechanical Pain Sensitivity

"Like before blunt fine rods will be pressed against your skin in a random order, you will be asked to rate each one on a scale of 0 to 100: 0 meaning no pain and 100 as the worst pain imaginable."

Dynamic Mechanical Allodynia

"As in the previous test a rod will be pressed onto your skin and you will be asked to rate it from 0 (no pain) to 100 (worst pain imaginable). In between each rod, you will be touched with a cotton wisp or a Q-tip or a brush and asked to rate these on the same scale".

Wind-Up Ratio

"Like the previous test, I will again press a single rod to your skin. Please rate the painfulness of this by giving a number from 0 (no pain) to 100 (worst pain imaginable). Any "sharp" or "stinging" sensation should be considered painful. I will now apply a series of 10 stimulations with the same rod at 1 second intervals. Once the entire series is over please rate the painfulness on the same scale by giving a number from 0 to 100".

Two Point Discrimination

"I will touch your hand with a tool at several times. Each time I would like you to tell me if you can feel one or two points".

Vibration detection threshold

"During this procedure, I will touch your skin with a Tuning Fork (a metal rod). Please immediately say "now" at the exact moment you no longer feel the vibrations."

Pressure Pain Threshold

"During this procedure, the algometer will be used to deliver pressure stimulation. We are primarily interested in the pain you experience as the pressure increases. We would like you to tell us when you first feel pain as a result of the pressure procedure. As soon as the device first produces a pain sensation, let us know – please say "pain" or signal with your hand. Do you have any questions?"

Cold pain threshold

"We are about to begin the water immersion procedure. This involves placing your dominant hand into the water bath up to your wrist, do not make a fist with your hand and try not to touch the sides or bottom of the machine. The water may feel quite cold, and the sensation it produces may be painful. After about 20 seconds, I will ask you to rate the intensity of pain that you are feeling in your dominant hand. If the pain in your hand becomes intolerable, please inform us by raising your opposite hand or saying "pain", and then remove your hand from the water. Do you have any questions?"

Electrocutaneous pain threshold

"During this procedure, the Digitimer will be used to deliver electrocutaneous pain sensation. We are primarily interested in the pain you experience as the current increases. We would like you to tell us when you first feel pain as a result of the procedure. As soon as the device first produces a pain sensation, let us know – please say "pain" or signal with your hand. Do you have any questions?"

Appendix D. Facial Units Removed from the Whole Analysis for all Stimuli

Table 29:

Facial units removed from the whole analysis for all stimuli

Cluster	Unit Number	Unit Description
Miscellaneous	AU21	Neck Tightener
	AD29	Jaw Thrust
	AD30	Jaw Sideways
	AD33	Blow
	AD34	Puff
	AD35	Suck
	AD36	Bulge
	AD37	Lip Wipe
Eyes	66	Cross Eye
Gross Behaviour	40	Sniff
	50	Speech
	80	Swallow
	81	Chewing
	84	Head Shake
	85	Head Nod
Movement	69	Eye Movement
	M68	Eye Movement
	M69	Eye Movement
	M83	Head Movement
	M55	Head Movement
	M56	Head Movement
	M59	Head Movement
	M60	Head Movement
	M61	Eye Movement
	M69	Eye Movement

Appendix E. Subsequent Facial Units Removed from Cold Pressor Stimuli Analyses

Table 30:

Facial unites removed for cold pressor sensation

Cold Pressor Sensation (CPS)		
Cluster	**Unit Number**	**Unit Description**
Upper	AU5	Upper Lid Raiser
	AU46	Wink
Lower Vertical	AU9	Nose Wrinkler
	AU10	Upper Lip raiser
	AU17	Chin Raiser
	AU27	Mouth Stretch
	AU16	Lower Lip Depressor
Lower Horizontal	AU20	Lip Stretch
Lower Oblique	AU13	Sharp Lip Puller
Lower Orbital	AU23	Lip Tightener
	AU24	Lip Pressor
	AU28	Lip Suck
Miscellaneous	AU8+25	Lip Towards Each Other
	AU31	Jaw Clencher
	AU38	Nostril Dilator
	AU39	Nostril Compressor
Head	57	Head Forward
Eyes	65	Wall Eye
Gross Behaviour	82	Shoulder Shrug
	91	Flash
	92	Partial Flash

Table 31:

Facial units removed for cold pressor pain

Cold Pressor Pain (CPP)		
Cluster	**Unit Number**	**Unit Description**
Lower Vertical	AU16	Lower Lip Depressor
Lower Orbital	AU22	Lip Funneler
	AU23	Lip Tightener
Miscellaneous	AU8+25	Lip Towards Each Other
	AU31	Jaw Clencher
	AU38	Nostril Dilator
	AU39	Nostril Compressor
Head	57	Head Forward
Eyes	65	Wall Eye
Gross Behaviour	82	Shoulder Shrug

Table 32:

Facial units removed for cold pressor tolerance

CPT		
Cluster	**Unit Number**	**Unit Description**
Lower Vertical	AU9	Nose Wrinkler
	AU27	Mouth Stretch
	AU16	Lower Lip Depressor
Lower Horizontal	AU14	Dimpler
Lower Orbital	AU22	Lip Funneler
	AU23	Lip Tightener
	AU24	Lip Pressor
Miscellaneous	AU8+25	Lip Towards Each Other
	AU31	Jaw Clencher
	AU38	Nostril Dilator
	AU39	Nostril Compressor
Eyes	65	Wall Eye
Gross Behaviour	82	Shoulder Shrug