Assessing physiological sensitivity in Post-Traumatic Stress Disorder

Aimee I. McKinnon

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A thesis submitted to Cardiff University for the degree of Doctor of Philosophy in Psychology

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Summary

People who have endured horrific events often bear predictable psychological harm. The symptoms of this harm can persist to produce a recognised clinical syndrome, Post-Traumatic Stress Disorder (PTSD). The lived reality of PTSD is a condition in which sufferers experience unbearable emotional reactions to traumatic reminders and exist in a persistent state of fear. Although the psychiatric and psychological construct of PTSD has been hotly contested, research and clinical opinion seem to converge around a state of enhanced sensitivity to threat, underpinned by chronic physiological hyper-arousal. This thesis has been concerned with the development of assessment measures that are sensitive to physiological hyper-arousal, including pupillometry and visual contrast sensitivity. In three experiments, a sample of 73 participants recruited from military, addiction and homelessness charity services were assessed for PTSD symptomology with the Clinician Administered PTSD Scale for DSM-V, and the self-report Impact of Event Scale-Revised. During passive viewing of emotive images, individuals with PTSD showed pupil responses that were influenced more by emotive stimuli than controls, and showed a reduced constriction of the pupil to light; revealing altered states of arousal. Due to methodological differences, a task assessing pupil responses to emotive sound clips failed to replicate this result. The assessment of visual contrast sensitivity revealed the heterogeneous nature of PTSD. Multi-dimensional assessment of symptom subscales showed that higher levels of re-experiencing symptoms were related to heightened visual sensitivity, but avoidant symptoms were related to lower sensitivity. Overall, the assessment of psychophysiological responses in PTSD demonstrated the utility of pupillometry for the assessment of PTSD, contributed to the literature on the regulation of the autonomic nervous system in PTSD, and highlighted the diversity of the clinical construct due to opposing effects of the symptom subscales.

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CHAPTER ONE

1.1 Post-Traumatic Stress Disorder: A History and Critical Analysis of a Construct

After her husband's return from war in Henry IV, Lady Percy wonders of him,

"*What is't that takes from thee*

Thy stomach, pleasure, and thy golden sleep?

Why dost thou bend thine eyes upon the earth,

And start so often thou sit'st alone?"

William Shakespeare, Act II Scene iii, in Henry IV, Part 1.

1.1.1 Abstract

This chapter presents the history and development of Post-Traumatic Stress Disorder (PTSD). The discussion is framed by the diagnostic construct developed by the American Psychiatric Association - the *Diagnostic and Statistical Manual for Mental Disorders* (DSM). The discussion begins with historic accounts of PTSD-like symptoms as a basis for construct validity, moves on to consider the development of theories of PTSD, followed by a critique of the validity of the diagnostic construct. Due to issues identified within each of these areas, the PTSD diagnostic construct has been criticised, in the extreme, as a "faddish postulate" that has "moved the mental health field away from, not toward, understanding the psychological responses to trauma" (McHugh & Treisman, 2007, p. 221). The crucial message from the issues in measurement is that empirical findings are only as strong as the clarity of the construct. When this construct is heterogeneous and lacking in validity it

becomes increasingly difficult to study a phenomenon in a meaningful way. However, whilst the definition of a 'traumatic' event and the diagnostic category classification process have some severe limitations, it is concluded that it still offers substantial heuristic value in the generation and continuity of research. This information and conclusion is used to inform the analyses within experimental chapters.

1.1.2 Introduction and Historic Context

Post-Traumatic Stress Disorder (PTSD) was introduced to the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) in 1980 (DSM-III; American Psychiatric Association, 1980), two years after introduction to the International Classification of Diseases (ICD-9; World Health Organisation, 1978). At this time, it was seen and felt to be a recognition of the psychological consequences of warfare in the aftermath of the Vietnam war (Gersons & Carlier, 1992). The disorder was originally conceptualised as a 'normal' response to extreme psychic trauma, however, this recognition was also one of abnormality and medical pathology which marked the beginnings of a structured approach to trauma assessment and intervention.

Until the late nineteenth century, the term 'trauma' was largely identified only with physical injuries (Young, 1997) but the concept and theory of psychological trauma predates the introduction of PTSD to the psychiatric manuals and has origins in theory such as, *Studies on Hysteria* (Breuer & Freud, 1957), the strength of the nervous system (Gray, 1964; Nebylitsyn, Rozhdestvenskaya, & Teplov, 1960; Pavlov, 1927), and the interruption of homeostasis caused by the stress response (Cannon, 1914). References to post-traumatic

reactions in the literature are often named to reflect the context at the time, for example, ‘compensation neurosis’ (Rigler, 1879) captures an increase in compensation claims being made after accidents working on the railways on introduction of compensation laws in Prussia. The disorder was later referred to as soldier’s heart, war neurosis and shell shock (Crocq & Crocq, 2000).

Despite being one of the newer categories of mental disorder within the official nomenclature, evidence of post-traumatic reactions have been found from analysis of historic sources. In Shakespeare’s play, *Henry IV*, Part I (2.3.86; as quoted above) Lady Percy complains of her husband’s behaviour on returning from war after regular involvement in mortal combat. Her account is in keeping with what could be considered a post-traumatic reaction, more than four centuries before the condition was first formulated (Bennet, 2011).

Although there was a definite propagation of post-war research efforts, the study of disorders of traumatic stress and human costs are by no means limited to soldiers. A first-person civilian account has been described by Daly (1983) from the diary of Samuel Pepys during the great fire of London in 1666. Six months after the fire, Pepys notes such post-trauma experience as:

> I did within these six days see smoke still remaining of the late fire in the City; and it is strange to think how to this very day I cannot sleep a night without great terrors of fire; and this very night could not sleep til almost 2 in the morning through thoughts of fire. (p. 66)

One repeated criticism of PTSD is that it creates a medical condition out of normal distress (McHugh & Treisman, 2007). Questions are raised here as to what defines the boundaries between a 'normal' and a 'disordered' stress response, where disordered indicates a need for medical assessment and intervention. Pepys's account of night terrors, loss of sleep and intrusive thoughts are among what are now termed 're-experiencing' and 'arousal' symptoms. Studies examining the aftermath of disaster confirm that a disordered response, defined by a categorical diagnosis of PTSD, is not as 'normal', or occurring consistently across individual, as first defined by DSM-III. One such study recruited 130 survivors of the Northridge, California earthquake in 1994. The study demonstrated that only 13% of the survivors of the quake met full PTSD criteria. However, 48% of the sample met the criteria for both re-experiencing and arousal symptoms, as Pepys may have. This indicates that whilst some symptoms of PTSD may be more commonly experienced, development of a full, chronic PTSD is not a common, or 'normal' response.

The core components of PTSD, the traumatic stressor (Criterion A); the re-experiencing symptoms, such as flashbacks, nightmares and intrusive memories (Criterion B); the efforts to avoid internal or external reminders (Criterion C); the alterations in mood and cognition (Criterion D); and the experience of hyper-arousal (Criterion E) are outlined in Table 1, below. These components are combined with conditions specifying the duration of symptoms (Criterion F), the need for the symptoms to cause distress and functional impairment (Criterion G), and for these symptoms to necessarily follow the traumatic event and not to be attributable to other causes (DSM-V; American Psychiatric Association, 2013). The development and change since introduction to DSM are also mapped by Table 1.

Table 1. *Mapping Changes in Diagnostic Criteria in DSM-III (1980), DSM III-R (1987), DSM-IV (1994), DSM-IV-TR (2000) and DSM-V(2013)*

Manual Criterion	DSM-III	DSM III-R	DSM-IV	DSM-IV-TR	DSM-V
A	The person has experienced an event that is outside the range of usual human experience and that would be markedly distressing to almost anyone.	The person has experienced an event that is outside the range of usual human experience and that would be markedly distressing to almost anyone, e. g. serious threat to one's life or physical integrity; serious threat or harm to one's children, spouse, or other close relatives and friends; sudden destruction of one's home or community; or seeing another person who has been or is being, seriously injured or killed as the result of an accident or physical violence.	The person has been exposed to a traumatic event in which both of the following have been present: The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others; the person's response involved intense fear, helplessness, or horror.	The person has been exposed to a traumatic event in which both of the following have been present: The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others; the person's response involved intense fear, helplessness, or horror.	The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, as follows: 1) Direct exposure. 2) Witnessing, in person. Indirectly, by learning that a close relative or close friend was exposed to trauma. If the event involved actual or threatened death, it must have been violent or accidental. 3) Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (e.g. first responders, collecting body parts; professionals repeatedly exposed to details of child abuse). This does not include indirect non-professional exposure through electronic media, television, movies, or pictures.
B	Re-experiencing; 4 symptoms, 1 for diagnosis	Re-experiencing; 4 symptoms, 1 for diagnosis	Re-experiencing; 4 symptoms, 1 for diagnosis	Re-experiencing; 7 symptoms, 1 for diagnosis	Re-experiencing; 5 symptoms, 1 for diagnosis
C	Avoidance; 7 symptoms, 3 for diagnosis.	Avoidance; 7 symptoms, 3 for diagnosis.	Avoidance; 7 symptoms, 3 for diagnosis.	Avoidance; 7 symptoms, 3 for diagnosis.	Avoidance; 2 symptoms, 1 for diagnosis.

D	N/A	N/A	N/A	N/A	Negative alterations in cognitions and mood; 7 symptoms, 2 for diagnosis.
E	Hyper-arousal; 6 symptoms.	Hyper-arousal; 6 symptoms, 2 for diagnosis.	Hyper-arousal; 5 symptoms, 2 for diagnosis.	Hyper-arousal; 5 symptoms, 2 for diagnosis.	Alterations in arousal and reactivity; 6 symptoms, 2 for diagnosis.
F	Duration of B, C, and D of at least one month.	Duration of B, C, and D of at least one month.	Duration of B, C, and D of at least one month.	Duration of B, C, and D of at least one month.	Duration of B, C, and D of at least one month.
G	N/A	N/A	The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.	The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.	The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
H	N/A	N/A	N/A	N/A	Exclude if the disturbance is due to medication, substance use, or other illness.
Specifier	Specify delayed onset if the onset of symptoms was at least six months after the trauma.	Specify delayed onset if the onset of symptoms was at least six months after the trauma.	Specify if acute (< 3 months) or chronic (≥ 3 months). Specify delayed onset if the onset of symptoms was at least six months after the trauma.	Specify if acute (< 3 months) or chronic (≥ 3 months). Specify delayed onset if the onset of symptoms was at least six months after the trauma.	Specify if acute (< 3 months) or chronic (≥ 3months). Specify delayed onset if the onset of symptoms was at least six months after the trauma. Specify if 1) Depersonalisation: experience of being an outside observer of or detached from oneself (e.g. feeling as if "this is not happening to me" or one were in a dream) and/or 2) Derealisation: experience of unreality, distance, or

distortion (e.g. “things are not real").

DSM Axis and Category	Axis-I, Anxiety Disorders	Axis-I, Anxiety Disorders	Axis-I, Anxiety Disorders	Axis-I, Anxiety Disorders	Axis-I, Trauma and Stressor-related Disorders

Note. The ‘Criterion’ column follows the lettering order of DSM-V. Criterion B-E encompass specific symptom categories. Total symptoms per category and number of symptoms required for diagnosis are indicated. DSM–III = Diagnostic and Statistical Manual of Mental Disorders (3rd edition); DSM-III-R = DSM (3rd edition, revised); DSM–IV = DSM (4th edition); DSM–IV-TR = DSM (4th edition, text revision); DSM–5 = DSM (5th edition). N/A indicates where a criterion was not included in a specific edition.

1.1.3 Theories of Post-Traumatic Stress Disorder

Theories of PTSD have been developed in line with major psychological models to explain the onset and maintenance factors for the disorder, and to distinguish PTSD from other mental illnesses for assessment and treatment. Cognitive theories consider PTSD to be a disorder of memory (Brewin, Dalgleish, & Joseph, 1996; van der Kolk, 2007) and a disorder in information processing, emotion and attention (see Buckley, Blanchard, & Neill, 2000 for a review). Behavioural theories consider PTSD to represent a disordered fear conditioning response (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Dębiec & Ledoux, 2004; Mahan & Ressler, 2012). Further accounts combine behavioural and cognitive conceptualisations (Foa, Steketee, & Rothbaum, 1989) to reconcile findings such as threat perception or appraisal during trauma predicting the onset of PTSD more effectively than actual threat. Biological theory focusses on brain, central nervous system and physiological arousal (e.g. van der Kolk, 2006) and many social factors have been implicated in the risk for PTSD (Brewin, Andrews, & Valentine, 2000). A broad review of theory in PTSD is discussed below. Of most relevance to experimental chapters within this thesis is the evidence relating to emotional processing and physiological responsivity, specific experimental evidence for which can be found within chapter introductions.

Cognitive theories of PTSD (e.g. Ehlers & Clark, 2000) form the basis for the cognitive behavioural therapy (CBT) treatment models. Cognitive theory poses that PTSD becomes chronic when an individual processes the traumatic event in a way that leads to a constant sense of serious, current threat termed ‘hypervigilance’. The pervasive feeling of being threatened and fearful arises because of: (1) excessively negative appraisals of the trauma and/or conditions arising due to the trauma and (2) a disturbance of autobiographical

memory. A change in appraisal and autobiographical memory is prevented by a series of problematic behavioural and cognitive strategies. Negative appraisals can concern any aspect of the traumatic event and its sequelae and lead to a persistent sense of current threat. The nature of the emotional response also depends on the particular appraisal (Beck, 1976) for example, appraisals concerning perceived danger ("nowhere is safe") lead to fear. Cognitive theory, including the SPAARS (schematic, propositional, analogue and associative representational systems see, Dalgleish, 2004; Dalgleish & Power, 2004; Power & Schmidt, 2004); model of emotion and emotional disorder proposes that negative emotion arises from a discrepancy between trauma-related information and the content of pre-existing mental representations (such as schemas).

Emotional processing (Foa & Kozak, 1986) is the modification of the memory structures underlying emotion and was first used to describe therapies for anxiety disorders. Emotional processing of fear is suggested to be critical to PTSD, and has formed the basis of exposure therapy. As mentioned above, consistent with the diagnostic features of PTSD (persistent negative emotional state and persistent inability to feel positive emotions, Criterion D, items 4 and 7) individuals often report intense negative emotion, whilst being unable to elicit and express emotion in other situations (Horowitz, 1986; Litz, Orsillo, Kaloupek, & Weathers, 2000). The emotional profile of PTSD revolves around intense fear and anxiety (Dalgleish & Power, 2004) and the elicitation of the chronic fear response is the core emotion-specific component of PTSD.

Appraisals occurring due to the traumatic event are not limited to fear, and individuals report strong experiences of numbing, anger, disgust, sadness, guilt and shame (Hathaway, Boals, & Banks, 2010). Horowitz (1986) conceptualised PTSD as the alteration between

intrusive recollections and numbing of emotional responsivity. Anhedonia, or the inability to experience pleasure and positive emotion, is therefore considered to be core to the PTSD concept by some, but has been criticised for overlapping strongly with depression. Glover (1992) suggests that numbing in PTSD can be distinguished as the absence of feeling, rather than the presence of depression or sadness. Feeny, Zoellner, Fitzgibbon and Foa (2000) explored the role of emotional numbing, dissociation and depression in PTSD in a follow up study of 161 sexual assault victims. Their findings supported a unique role for numbing in contributing to the development of later PTSD, after controlling for both dissociation and depression.

Experimental evidence looking at numbing symptoms demonstrates that individuals with PTSD both self-report less intense feelings toward happy faces, and show lower activation to happy faces (relative to neutral faces) in the ventral striatum during imaging (Felmingham et al., 2014). A study conducted by Litz et al. (2000) assessed 'emotional behaviour' in PTSD. The study displayed ideographic trauma primes (combat videos in a sample of Vietnam veterans) and assessed responses to emotional images (positive, neutral and negative) after playing the video. The authors found that the PTSD group could be distinguished through higher levels of negative affectivity throughout and showed suppressed expressive facial reactions to positive stimuli. However, the PTSD group showed no augmentation of response to negative stimuli after trauma priming, but did display increased heart rate and skin conductance responses to all conditions. The authors indicate that emotional deficits in PTSD are due to the automatic preparation for threat in any uncertain emotional context. A study employing Lang's Looking at Pictures test (Lang, Greenwald, Bradley, & Hamm, 1993) assessed self-reported arousal in 21 Bosnian refugees with PTSD and found, in both males and females with PTSD, pleasant pictures were rated as almost

completely non-arousing (Spahic-Mihajlovic, Crayton, & Neafsey, 2005). Studies which are based on methodology other than self-report are limited. However, there is evidence relating to lack of positive stimulus attentional bias in individuals with high levels of anxiety (Chen, Clarke, Watson, MacLeod, & Guastella, 2014). Positive stimuli conditions in studies of PTSD appear relatively uncommon in comparison to negative stimuli, with most of the literature focussed on threat reactivity.

High levels of negative affectivity are also common to many psychiatric disorders, and there is evidence of significant diagnostic overlap between PTSD and major depression, with PTSD and comorbid PTSD/depression appearing indistinguishable in some studies (O'Donnell, Creamer, & Pattison, 2004). A meta-analysis of attention bias in anxiety (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007) showed threat-related attentional bias to be specific to anxious versus non-anxious individuals, including studies of PTSD (k = 22, Cohen's d = 0.36, p. 10). However, this feature is not unique to PTSD as attentional bias to threat was evident across anxiety disorders. A challenge for performance based assessment measures in PTSD is the ability to discriminate PTSD from disorders of anxiety. Research suggests that another key feature of PTSD, intrusive recollections, are also common to other psychiatric disorders, such as obsessive compulsive disorder, eating disorder, and psychosis (Brewin, Gregory, Lipton, & Burgess, 2010). Evidence suggests that re-living the past in the present as a sensory-bound representation distinguishes PTSD from other disorders (Brewin, 2014). This area highlights the challenges for theories of PTSD in identifying disorder-specific rather than trans-diagnostic indicators.

The common thread within both conflicting and compatible theories of PTSD is that emotional regulation of fear responses are key to the disorder (Williamson, Porges, Lamb, &

Porges, 2015). Studies of biological factors in the acquisition and maintenance of PTSD assess the neural, psychophysiological and behavioural markers of fear, which can either allude to mechanisms or add to the evidence suggesting alterations in arousal in PTSD (Criterion E). Dysregulation of systems which organise the stress response can offer insights into both the effects of PTSD and biological 'vulnerability' factors within certain populations (Sherin & Nemeroff, 2011). There is a vast amount of evidence to suggest the mechanisms of fear and the stress response lies within altered functioning of the autonomic nervous system (see Sherin & Nemeroff, 2011; Williamson et al., 2015 for reviews), the dysregulation of which serves to disrupt a myriad of responses, from emotion and cognition to cardiovascular health. Chronic and acute emotional arousal states occur due biological, psychological and environmental factors. An integrated biopsychosocial approach to PTSD has provided evidence for the lasting effects of traumatic stress on brain areas implicated within the stress response (Bremner, 2006), the hypothalamic pituitary adrenal (HPA) axis, and the autonomic nervous system (Brotman, Golden, & Wittstein, 2007). Pitman, Orr and colleagues (e.g., Orr, Pitman, Lasko, & Herz, 1993; Orr, Metzger, & Pitman, 2002; Pitman et al., 2001; Pitman, Orr, Forgue, de Jong, & Claiborn, 1987; Shalev, Orr, & Pitman, 1993) have worked extensively on physiological responsivity in PTSD and have demonstrated the utility of physiological measures across methods and PTSD acquisition types. Neuroscience research strongly implicates a role for the amygdala in hyper-arousal (see Weston, 2014 for a review of biological evidence and theoretical model of hyper-arousal), with a multifunctional impact on other brain regions, including the visual cortex. Visual perception is suggested to be more sensitive in PTSD, as evidenced by attentional studies assessing perceptual biases for trauma-related stimuli (Kleim, Ehring, & Ehlers, 2012). fMRI studies indicate that the neural basis for the experience of visual flashbacks recruits the early visual cortex. For example,

Whalley et al. (2013) found that, compared with ordinary episodic memory which recruited the medial temporal lobe, the experience of flash backs was associated with increased activity in the sensory and motor areas. A longitudinal study of veterans demonstrated that individuals with PTSD with a worsening course demonstrated significant brain atrophy throughout the brain, including the insula, anterior cingulate, dorsolateral prefrontal cortex, and anterior temporal lobe. The insula particularly is implicated in regulation of parasympathetic and sympathetic nervous systems, which may allude to a mechanism of the overactive sympathetic response, underactive parasympathetic response, or both (van der Kolk, 2006). Van der Kolk synthesised the clinical implications of neuroscientific research into PTSD by suggesting that traumatised individuals "lose their way in the world" due to intense emotional reactions, failure to integrate sensory experiences, failure to communicate in words, and failure to modulate physiological arousal, in addition to impairments in attention and memory which cause an inability to engage with the present.

1.1.4 Validity in Psychiatric Diagnosis

The introduction of rule-based diagnostic criteria has led to gains in diagnostic agreement, improved communication, statistical estimates for prevalence and prognosis and an empirical literature and medical language in which treatment of mental illness and disorder can be discussed and evaluated. These gains are undeniably reflective of the utility of psychiatric diagnosis (although, see Timimi, 2014 for a summary of the negative effects of psychiatric diagnosis), and are representative of a move from an unstructured system to an evidence-based system which has supported the growth of evidence. Although ongoing debate and criticism is necessary, support for psychiatric diagnosis appears to be faltering,

both within clinical practice and research settings. One of the major issues with diagnostic criteria is validity, and PTSD is no exception to this issue.

Within psychology, the American Psychological Association's distinctions between content, criterion-related and construct validity are usually adopted (American Psychological Association, 1966, see Table 2) with a particular emphasis on the validity of psychometrics for psychological testing. Psychiatry has borrowed terms from psychometric theory, with criterion validity appearing to be the most important. Kendell and Jablensky (2003) suggest that the meaning of 'validity' in the context of psychiatric diagnosis has never been adequately defined. Validity is not an inherent property of a test or a construct and not something which is measured by a single metric, rather, validity is a judgement (Lissitz, 2009).

Table 2. *Definitions of Criterion, Construct and Content Validity, Including Subtypes*

Criterion Validity	In 1966 the APA merged the concepts of predictive and concurrent validity to represent a single category. Criterion validity refers to the extent to which a measure is related to an outcome.
Construct Validity	The correspondence between test-items and symptoms of a clinical syndrome the test purports to assess. "Evidence of construct validity is not found in a single study; judgments of construct validity are based upon an accumulation of research results" (APA, 1966, p. 30)
Discriminant Validity	Is a subtype of construct validity, and refers to whether the test or theoretical construct can be differentiated from other constructs. Campbell and Fiske (1959) suggest that tests can be invalidated by showing too high a relatedness to other tests from which they are

	intended to differ (p. 80).
Convergent Validity	Is a subtype of construct validity used to assess whether measures of constructs that theoretically should be related to each other are, in fact, observed to be related. Campbell and Fiske (1959) define this as a confirmation of construct by independent measurements.
Content Validity	Lawshe (1975) defines this as the extent to which there is overlap between a test and performance. Cronbach and Meehl (1955) define content validity as the demonstration that test items are sampled from a population in which the investigator is interested in.
Face Validity	Face validity is not a related to statistical assessment, but is a general assessment of whether a test superficially appears to measure the construct specified.

1.1.4.1 Validity of the Post-Traumatic Stress Disorder Diagnostic Construct

Analysis of historic sources gives validity to the construct of PTSD, indicating correspondence to 'real world' phenomena prior to its introduction to DSM, or the International Classification of Diseases (ICD-10; World Health Organisation, 1992). However, the construct has continually evolved since introduction in 1980. This evolution has often been controversial (e.g. Brewin, Lanius, Novac, Schnyder, & Galea, 2009; Hoge et al., 2016; McNally, 2009; Rosen, Spitzer, & McHugh, 2008; Spitzer, First, & Wakefield, 2007) and each update has been subject to both speculative and post-publication criticism. The DSM-III diagnostic criteria for PTSD were revised in DSM-III-R (1987), DSM-IV (1994), DSM-IV-TR (2000) and DSM-V (2013) and these revisions are outlined in Table 1. As can be seen from the table, an area which has undergone extensive revision is Criterion A.

DSM diagnostic categories are otherwise agnostic to aetiology, meaning that the origins of a problem are not necessarily based in a specific event. PTSD is unique in that it is set to necessarily occur after a specific set of traumatic stressors (see Table 1, Criterion A for variants of this specification through the evolution of the DSM). The idea that pathology could be entirely explained by an event, rather than the characteristics of an individual, was immediately controversial on introduction and has remained so (Brewin et al., 2009). The construct rests upon the assumption that a specific class of traumatic events are linked to a distinct clinical syndrome. In an evaluation of the core assumptions of PTSD, Rosen and Lilenfeld (2008) summarise evidence suggesting that symptoms can follow events such as marital disruption, affairs, and divorce; collapse of adoption arrangements; bereavement; employment and financial crisis; loss of cattle due to foot and mouth disease; breaking up with a best friend; and even in response to frightening Halloween television programmes. These findings raise concerns as to the necessity of Criterion A. However, most studies are limited to screening assessments, rather than clinician assessment, which does not consider other necessary conditions such as clinically significant distress, impairments in functioning and duration. Brewin and colleagues (2009) recommended, prior to the introduction of DSM-V, that Criterion A should be removed from DSM-V.

There is research evidence to suggest that the validity of Criterion A is limited within studies using a full diagnostic assessment. For example, Bodkin, Pope, Detke, and Hudson (2007) found an equivalent rate of trauma symptoms in individuals with and without experience of a Criterion A stressor seeking treatment for major depression. Similar results have been found among people with social phobia (Erwin, Heimberg, Marx, & Franklin, 2006) and experiences of trauma are now recognised as potential precipitating factors in a wide range of mental illness symptoms, such as Borderline Personality Disorder (Herman,

Christopher, & Van der Kolk, 1989), psychosis (Bendall, Jackson, & Hulbert, 2010; Morrison, Frame, & Larkin, 2003) and an array of adverse mental health outcomes (for examples see, Golding, 1999; Steel, Silove, Phan, & Bauman, 2002). Even when an individual encounters horrific, life-threatening events, studies find that pre and post incident factors contribute more to post-trauma morbidity than does the magnitude of the presumed aetiological trauma. For example, a meta-analysis conducted by Brewin, Andrews and Valentine (2000) found pre-trauma factors such as previous psychiatric history, reported childhood abuse, and family psychiatric history have uniform predictive effects, whereas the predictive effects of factors such as education, previous trauma, general childhood adversity, gender, age and race vary from study to study and are dependent on populations and methodology employed. Post trauma factors, such as post-war social support, has also been found to be a contributing factor to the development of PTSD (King, King, Fairbank, Keane, & Adams, 1998). There is now wide acceptance that exposure to a trauma is not always sufficient to explain the development of PTSD and that both environmental factors and individual vulnerability factors have a role to play in understanding this condition (Yehuda, 1999).

As alluded to in section 1.1.3, discriminant validity is also an issue which is increasingly plaguing the validity and utility of the diagnostic construct. Diagnostic permutations have been increasing with each new edition of the DSM. In one of the first systematic studies, Galatzer-Levy and Bryant (2013) calculate that the addition of new symptoms to DSM-V has increased the level of heterogeneity from 79,794 symptom combinations within DSM-IV to 636,120 ways to have PTSD in DSM-V. Similarly, Young, Lareau and Pierre (2014) suggest that PTSD often occurs in response to poly-trauma with co-morbidity, and suggest the number of symptom combinations in full polytrauma is over one-

quintillion. These figures suggest mass diversity in responses to trauma, diversity within individuals categorised under the umbrella of 'PTSD' and inevitable overlap with other disorders.

Studies supportive of the validity of PTSD suggest that there are so-called 'primary markers' for the disorder. Reynolds and Brewin (1998) matched individuals suffering from either PTSD or depression and non-clinical controls and found flashbacks to be a distinctive feature of PTSD. Another primary marker for the disorder, partly behind the rationale for moving PTSD from the Anxiety Disorders category to a new category (Trauma- and Stressor-Related Disorders) in DSM-V is the role of emotional experience of fear over the course of PTSD (Resick & Miller, 2009). PTSD diagnosis can be used to predict outcomes and functional impairment. For example, a longitudinal study of children with a PTSD diagnosis over 2 years found that a diagnosis at time 1 significantly predicted diagnosis 2 years later (Scheeringa, Zeanah, Myers, & Putnam, 2005). Although, there was variation in continuity, with re-experiencing symptoms decreasing and avoidance and numbing symptoms increasing. This finding alludes to both the predictive validity and test-rest reliability of the disorder, but also hints at the heterogeneity within the symptom subscales.

1.1.5 Conceptualisation of Post-Traumatic Stress Disorder in Experimental Chapters

As discussed above, the validity of contemporary diagnostic categories is in question due to limited evidence of natural boundaries between disorders (Kendell & Jablensky, 2003) and a lack of a homogenous construct. It is important to note that questioning the validity of diagnostic constructs does not question or invalidate suffering or distress, but questions the

utility of a construct in which two individuals assessed as having the same disorder can be in distress due to completely divergent symptoms. Three and a half decades of research has yielded much evidence, but no objective indicators of, or specific pharmacotherapy for PTSD (Schmidt & Vermetten, 2017). Consistent with the heterogeneous nature of the disorder, individual studies of symptoms and responses within PTSD vary greatly in their findings (Etkin & Wager, 2007). Individual factors including age, gender, education, IQ, discrete versus multiple trauma, type of trauma, and time since trauma all complicate sampling. Study methodology and operationalisation of PTSD also vary greatly, but the majority of studies seem to opt for group designs, comparing individuals with PTSD to those without. Researchers are increasingly assuming variation in symptoms to be continuous, rather than categorical. For example, the Research Domain Criteria (Insel et al., 2010) has taken a radical departure from DSM in attempting to encourage research based on dimensions of observable behaviour and neurobiological measures (Cuthbert, 2014). This viewpoint also emphasises that psychiatric disorders share many more commonalities than differences, and are therefore questioning the validity of contemporary classifications. A dimensional view of PTSD reflects the extreme of a stress response continuum, rather than a unique clinical syndrome that can be discretely differentiated from other disorders. Evidence for a taxonomic structure for PTSD is mixed. The use of the categorical cut off is important and rightly contested and debated, as it defines and determines the point at which an individual is considered to need treatment and their subsequent rights due to reduced functional capacity. However, a number of studies provide strong evidence for a dimensional latent structure of PTSD (Broman-Fulks et al., 2006; Kramer et al., 2016; Ruscio, Ruscio, & Keane, 2002). Recent research by Kliem et al. (2016) analysing the latent structure of PTSD in a German population (N = 1,212) found support for a categorical solution for PTSD, using a core item-set approach made up of

3 cardinal factors (re-experiencing, avoidance and hyper-arousal). In comparison, when the authors used a full four factor model (re-experiencing, avoidance, numbing and hyper-arousal) they found that symptoms differed in degree, rather than in kind. The authors conclude that this supports the recommendations from the ICD-11 expert committee to adopt this solution to PTSD diagnosis (Maercker et al., 2013). Brown and Barlow (2005) suggested the introduction of dimensional severity ratings, in addition to categorical cut offs and diagnoses to address limitations in the diagnostic approach. This is the approach adopted herein.

The following experimental chapters will consider the construct of PTSD on both a categorical diagnostic basis and a continuous dimension of symptom severity. The experimental paradigms aim to assess the effect of PTSD diagnosis and increasing symptom severity on indices of performance in psychophysiological pupillometry and perception tasks. Multi-dimensional analyses are used to assess the impact of PTSD symptom subscales on performance. The overarching aim of these experimental chapters was to develop an objective assessment which is sensitive to diagnostic status and symptom severity, to assess the potential utility of such performance or assessment measures within PTSD, and contribute to the knowledge base concerning arousal and emotional processing after traumatic stress.

CHAPTER TWO

2.1 The Assessment of Post-Traumatic Stress Disorder

2.1.1 Abstract

Psychometric properties are used as indicators of the validity and the reliability of an instrument and are crucial to both forming psychological and diagnostic assessments, and for the replicability of research. The properties of each of the psychometric measures used within experimental chapters are discussed below. These studies employ the use of the Clinician Administered PTSD Scale for DSM-V (CAPS-V; Weathers et al., 2013a), the Impact of Event Scale-Revised (IES-R; Weiss & Marmar, 1997), the Life Events Checklist for DSM-V with extended Criterion A Assessment (LEC-V; Weathers et al., 2013b), the State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970), and the Harm Avoidance Scale of the Temperament and Character Inventory (TCI; Cloninger, Przybeck, & Svrakic, 1994). Psychometric adequacy is demonstrated for each of the instruments. The use of multiple measures is also used to demonstrate construct validity. Sample demographics and relationships are discussed to inform sampling strategies for future research, and the general study procedures are outlined. Findings from the sample of participants recruited from addiction, military, homelessness and women's shelter third sector services suggest the prevalence of traumatic stress is higher than that reported in the general population and, within these services, self-reported experience of assessment and treatment of traumatic stress is low.

2.1.2 Assessing Psychological Trauma and Post-Traumatic Stress

Assessment of epidemiology, diagnosis, course, co-morbidity and treatments for PTSD require valid and reliable tools for assessment. The critical role of psychometrically stable assessment methods was highlighted during the first extensive epidemiological study of PTSD, The National Vietnam Veterans Readjustment Study (NVVRS; Kulka et al., 1988). When the contract for this study was awarded in 1984 there were no validated measures of PTSD in existence, so the authors were required to select and validate measures to distinguish cases from non-cases. The gold-standard for the assessment of a DSM based diagnosis of PTSD is a structured assessment administered by a clinician, the CAPS-V (Weathers et al., 2013a), but many other measurement tools exist (for a full review of assessment types see, Wilson & Keane, 2004). The experimental chapters include the use of the CAPS-V alongside additional psychometric measures to assess construct validity and the psychometric properties of each are discussed below.

2.1.3 The Clinician Administered PTSD Scale for DSM-V

The Clinician Administered PTSD Scale for DSM-V (Weathers et al., 2013a) is the gold standard in PTSD assessment. The CAPS-V is a 30-item structured interview that can be used to assess for a current diagnosis of PTSD (symptoms within the last month), assess the worst ever month, assess symptoms within the past week, or make a lifetime diagnosis of PTSD. The 20 symptom questions directly correspond to the DSM-V symptom criteria and, in addition to symptom assessment, questions target the onset and duration of symptoms, subjective distress, impact of symptoms of social and occupation functioning, include an option for assessing a change in symptoms from a previous assessment, assess overall

response validity, overall PTSD severity, and specifications for a dissociative subtype (depersonalisation and derealisation).

For each question, the interviewer follows explicit and structured standardised questions and probes. Administration requires the identification of a Criterion A traumatic event. Within the following experimental chapters, the Life Events Checklist (LEC; Weathers et al., 2013b) with extended DSM-V Criterion A assessment was considered to be the most systematic approach to assessing Criterion A and the use of this tool with the CAPS-V is recommended by Weathers et al. (2013a). The CAPS-V was designed to be administered by clinicians, clinical researchers, or appropriately trained paraprofessionals with a working knowledge of PTSD. The authors report that the full interview takes 45-50 minutes to administer and, consistent with this, interviews took between 40 – 60 minutes.

Within the current sample, the internal consistency based on the 56 interviews conducted was very high (Cronbach's alpha = .95). The inter-rater reliability of the CAPS-V measure has been assessed to account for the fact that, although trained, the researcher administering the diagnostic interview was not a registered clinician and official inter-rater reliability statistics have not been published yet. An existing study using the CAPS-V (Forbes et al., 2015) took 5% of the sample and found the diagnostic consistency on the CAPS-V was 100%. Inter-rater reliability (Pearson's *r*) for the sum of the frequency and intensity items for each symptom ranged from 0.83 for symptom D3 (distorted blame of self or others) to 1.00 for symptoms B3 (flashbacks) and C2 (avoidance of external reminders). Nash et al. (2015) took a random 15% of their sample and suggest an intra-class correlation (ICC) of .99 – almost perfect. To provide an estimate of inter-rater reliability for the following experimental chapters, a full transcript of a randomly sampled 18% (*n* =10, 6 male) of individuals (with

severity scores above 0) was written verbatim during interview, scored, entered in to a database, and then transcribed onto a clean form without scoring to be second rated. The second-assessor was a registered consultant clinical and forensic psychologist (Professor Nicola Gray). The researcher completed the official training modules for the CAPS-V and the second-assessor received formal training in CAPS assessment.

Many studies do not report inter-rater reliability (e.g. Metrik et al., 2016), but those that do appear to take a sample of 5 – 15% of interviews and use a second-assessor who is blind to the original score (for examples of reliability research in PTSD see, Bovin et al., 2016; Bryant et al., 2011; Carty, O'Donnell, Evans, Kazantzis, & Creamer, 2011). Although it is more common to assess inter-rater reliability through an audio-taped interview, this approach was not taken for ethical review purposes and concerns that being audiotaped would discourage participation and complicate recruitment.

The IRR sample consisted of 10 individuals with severity scores ranging between 2 – 59 (M = 30, SD = 20). All individuals met criterion A, with complete agreement between assessors (Cohen's κ = 1.0). Seven individuals met the criteria for a current diagnosis on PTSD, with complete diagnostic status agreement between assessors (Cohen's κ = 1.0). Reliability was assessed through intra-class correlation statistics (ICC; Shrout & Fleiss, 1979) and results are presented in Table 3. Through the 10 individual interviews, ICC values ranged between .78 – 1.0. There was complete agreement between ratings of functional impairment (level of distress, social impairment and occupational impairment) (Cohen's κ = 1.0). Difference scores were calculated to assess any systematic bias between the interviewer and the second assessor. Out of 200 possible item scores, the interviewer gave a one-point higher score 20 times and scored two-point higher item score once. The second assessor gave a score

which was one-point higher than the interviewer 8 times. This suggests that the interviewer tended to allocate slightly higher scores than the second assessor. It is suggested that this is due to the additional in-interview cues, such as emotional arousal and distress, that are not available whilst scoring vignette style interviews. Overall, the inter-rater reliability was excellent.

Table 3. *Intra-Class Correlations to Assess Inter-Rater Reliability in a Sample of 10 CAPS-V interviews*

	Items 1 – 20	Scale B	Scale C	Scale D	Scale E	Total Score
ICC	.96	.95	.97	.96	.97	.99

2.1.4 The Impact of Event Scale-Revised

Trauma psychometrics were among the most commonly administered measures by traumatic stress professionals (Elhai, Gray, Kashdan, & Franklin, 2005), with the Impact of Event Scale-Revised (IES-R; Weiss & Marmar, 1997) reported as the most commonly used within clinical practice. The creation of the original IES (Horowitz, Wilner, & Alvarez, 1979) predates the inclusion of PTSD to the DSM and was formed of intrusive and avoidant scales. The IES-R was updated for the DSM-IV to include the hyper-arousal scale, but no update exists for DSM-V. The measure was included within experimental chapters to provide some continuity from previous research into the PTSD construct, as defined by DSM-IV, and to provide an estimate of self-reported symptoms, rather than researcher assessed symptoms.

The IES-R is a 22 item self-report questionnaire measuring frequency of symptoms of posttraumatic intrusion (n = 7), avoidance (n = 8) and hyper-arousal (n = 7) occurring over the past seven days, measured on a 5-point Likert scale from 0 – 4, with a maximum score of 88. Higher scores indicate higher symptom severity. Previously reported internal consistency is high (Cronbach's a = 0.79 – 0.92) and test-retest reliability is also excellent (r = .89 – 94) (Beck et al., 2008). The IES-R possesses face validity as a clinical measure of post-traumatic distress, though it should be emphasised that it is not a measure of PTSD diagnostic status, as it does not consider the specificity of Criterion A, symptom duration or functional impairment and subjective distress.

Within the current sample, the internal consistency based upon 74 valid assessments was very high (Cronbach's a = .96). The construct validity can be assessed by comparison of IES-R and CAPS-V total severity score (see Table 4). Correlations were only produced here for individuals meeting Criterion A.

2.1.5 The Life Events Checklist with Extended Criterion A Assessment for DSM-V

The LEC-5 is a self-report measure designed to screen for potentially traumatic events in a respondent's lifetime (Weathers et al., 2013b). The LEC-V assesses exposure to 16 events known to potentially result in PTSD or distress and includes one additional item assessing any other extraordinarily stressful event not captured in the first 16 items. Previous versions of the LEC have been shown to have adequate psychometric properties in both clinical and non-clinical samples (Gray, Litz, Hsu, & Lombardo, 2004) but there are no existing psychometric properties for the LEC-V. Within the following experimental chapters,

the LEC was solely used to establish the presence a Criterion A stressor, so the lack of psychometric properties is not considered to be a limitation.

The LEC and criterion A assessment were used to guide the assessment of PTSD. The respondent was asked to identify, at the end of the LEC, the single most stressful thing which had ever happened to them, be it either a single event or multiple closely related events. The criterion A inquiry then followed. Individuals who did not satisfy the conditions of the criterion A assessment were not asked to complete the CAPS-V interview (N = 18), but still completed the IES-R. An example of a non-Criterion A trauma is bereavement or an injury in which there was no threat to life or serious damage (perceived or actual). The evident limitation of this method is the potential for the interviewer to miss a potentially traumatic event, meaning that the individual would otherwise be categorised as 'trauma exposed', or assessed with some symptoms. The experimental chapters include administration of the IES-R assessment to all participants, regardless of the presence or absence of Criterion A trauma, for inclusion in dimensional analyses, and to explore the effects of including these individuals within dimensional analyses.

2.1.6 The State-Trait Anxiety Inventory

The State Trait Anxiety Inventory (STAI; Spielberger et al., 1970) is a widely used anxiety questionnaire, based on a 20-item state (STAI-S) and a 20-item trait anxiety (STAI-T) subscale, measured on a 4-point Likert scale from 1 – 4 with a maximum score of 160. Higher scores on both subscales indicate the presence of more anxiety. The STAI was administered to examine the convergent validity of the IES-R and to assess the ability of

PTSD symptomology to explain variation in performance measures used within experimental chapters over and above the impact of anxiety. Good internal consistency has been reported for the STAI (α ranging from .86 to .95; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) and the scale's test-retest reliability ranges from .75 to .86 for re-test intervals of 30 days or less (Spielberger et al., 1983). Convergent validity of the STAI-T and other measures of trait anxiety has been noted (e.g., Bieling, Antony, & Swinson, 1998).

Within the current sample of 74 complete STAIs the internal consistency of the State Anxiety scale is very high (Cronbach's alpha = .90), as is the Trait Anxiety scale (Cronbach's alpha = .96) and the full scale (Cronbach's alpha = .96). Correlations between the two subscales and full scale are reported in Table 4.

2.1.7 The Temperament and Character Inventory and Harm Avoidance

The Temperament and Character Inventory (Cloninger et al., 1994) is a 240-item questionnaire, answered on a two-point ('true' or 'false') scale. The TCI measures seven personality dimensions; Novelty Seeking, Harm Avoidance, Reward Dependence, Persistence, Self-Directedness, Cooperativeness, and Self-Transcendence. Harm Avoidance, the scale of interest within the current research, is comprised of 35 items forming four subscales; Anticipatory Worry, Fear of Uncertainty, Shyness with Strangers, and Fatigability and Asthenia ('weakness'). Harm Avoidance has strong correlations with measures of the trait Neuroticism (De Fruyt, Van De Wiele, & Van Heeringen, 2000) as measured by the NEO-PI-R (Costa & MacCrae, 1992).

Cloninger's model of temperament is based on the psychobiological basis for personality and trait emotional reactivity, considering emotional responses such as fear, anger and attachment to be biologically based, and aims to capture domains of personality specifically related to psychopathology (Cloninger, Svrakic, & Przybeck, 1993). The Harm Avoidance scale (HA scale) is a measure of temperament or trait and evidence supports the stability of this trait over time (Josefsson et al., 2013). Though no proxy measures can exist for PTSD due to the necessity of a specific traumatic event, personality-based approaches can provide a dimensional model of PTSD vulnerability (Jakšić, Brajković, Ivezić, Topić, & Jakovljević, 2012). Harm Avoidance has also been shown to be linked to PTSD symptomology (e.g. Evren, Dalbudak, Cetin, Durkaya, & Evren, 2010; Jakšić et al., 2012; Richman & Frueh, 1997; Yoon, Jun, An, Kang, & Jun, 2009). In cross sectional samples, Harm Avoidance has shown to be higher within a PTSD sample (Evren et al., 2010) and negatively associated with resilience to stress (Simeon et al., 2007). Yoon and colleagues (2009) have demonstrated that the severity of PTSD symptoms, as measured by the IES-R, were significantly associated with Harm Avoidance scores, but not with general anxiety. This approach suggests that the use of the HA scale in studies of traumatic stress can have discriminant predictive power, in that it measures a personality structure which is distinct from anxiety but which shares variance with symptom severity. Longitudinal samples have also demonstrated that a temperament which is high in Harm Avoidant traits conveys a risk for later development of PTSD. For example, Gil (2005) found that higher scores on the HA scale was positively associated with the risk for developing PTSD in a sample of college students exposed to a bomb attack.

Within experimental chapters the HA scale has been used in isolation, rather than the relevant scale questions being dispersed throughout the TCI. Using one scale can limit the

extent to which the validity and reliability of the scale, as established during development, can be taken for granted. The HA scale has been used alone in previously published work. For example, Most and colleagues (2005; 2006) used the scale to predict the degree of cognitive control during an emotion-induced blindness task. However, the authors did not estimate the reliability of the scale used alone, but their use of the HA scale to predict task performance and neural correlates is indicative of the predictive validity of the scale used alone. Within the current sample it is possible to report on the internal consistency (Cronbach's Alpha), the concurrent validity and the construct validity. The latter two can be assessed by looking at the relationship between the HA scale and symptom severity and measurements of interest.

Within the samples reported in the development of the TCI the values for reliability on the HA scale are high (Cronbach's alpha = .87 – .89) (Cloninger et al., 1994, p. 81). Within the current sample of 71 complete HA scale questionnaires, the value is also very high (Cronbach's alpha = .94), demonstrating excellent internal consistency. The relationship between the HA scale and psychometric variables of interest are represented in Table 4 and, as can be seen, there is a high level of relatedness between the HA scale and measures of interest, replicating previous findings discussed above and suggesting validity.

2.1.8 Medication score

Use of prescription psychotropic medication is common in clinical samples targeted for participation in psychological and psychiatric research. Psychotropic medications are any prescription medications with the potential to alter the mind, emotions, or behaviour and

broadly include anti-psychotic, antidepressant, anti-obsessional, anti-anxiety, anti-panic, stimulant, and mood-stabilising agents. Following on from preparatory work in a sample of psychiatric inpatients, a review of the effects of psychometric medications on performance indices used within the experimental chapters was conducted (see Appendix A). An outline of medication use in this sample is presented in Table A20, as are supplementary analyses for medications and performance outcome measures. For descriptive purposes, the approach taken was to quantify the amount of prescribed (and adhered to) medication reported by each participant, following the six categories listed above, with the addition of opiate analgesic medications. All individuals taking any form of opiate medication (illicit or prescribed) were excluded from experimental chapters. For the medication score, an individual was assigned one 'point' per medication prescribed and taken in the last 48 hours. Scores ranged from 1 to 5, with modal and median values of 0. Relationships between medication score and psychometric measures are displayed in Table 4. As expected, there were relationships between this medication score and all measures of psychopathology, bar total potential trauma, suggesting that individuals who were prescribed more medication had higher levels of psychopathology. The medication score was unrelated to performance measures over the three experiments, and these measures are reported in correlation tables within specific chapters (Table 11, Table 14 and Table 17). Supplementary analyses exploring specific effects of medication are reported in Appendix B.

2.1.9 Wechsler Abbreviated Scale of Intelligence

The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) two-subscale assessment was used to estimate intelligence quotient (IQ). The two-subscale

version takes around 15 minutes to administer and consists of verbal (oral word definitions to assess verbal concept formation) and performance subscales (matrix reasoning to assess perceptual organisation and broad visual intelligence). The measure produces an estimate of full scale IQ (FSIQ). IQ was well distributed within the sample (see Table 6 and Table 8) and there were no relationships between IQ and any measured variables, except for education level, as would be expected.

Table 4. *Zero-Order Correlations Between Psychometric Measures within the Whole Sample (*N = *56 – 73)*

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. Harm Avoidance	-														
2. State Anxiety	.51**	-													
3. Trait Anxiety	.72**	.71**	-												
4. Total Anxiety	.68**	.90**	.90**	-											
5. IES-R Intrusion	.62**	.43**	.43**	.55**	-										
6. IES-R Avoidance	.64**	.51**	.51**	.60**	.76**	-									
7. IES-R Hyper-arousal	.63**	.29*	.29**	.46**	.79**	.69**	-								
8. IES-R Total	.70**	.45**	.44**	.59**	.93**	.90**	.91**	-							
9. CAPS-V Intrusion Severity	.60**	.41**	41**	.53**	.88*	.70**	.77**	.87**	-						
10. CAPS-V Avoidance Severity	.53**	.42**	.42**	.45**	.58**	.77**	50**	.69**	.64**	-					
11. CAPS-V Negative Cognition Severity	.64**	.56**	.56**	.62**	.74**	.77**	.64**	.80**	.76**	.75**	-				
12. CAPS-V Hyper-arousal Severity	.50**	.54**	.45**	.50**	.65**	.60**	.71**	.73**	.72**	.54**	.75**	-			
13. CAPS-V Total Severity	.65**	.53**	.53**	.61**	.82**	.79**	76**	.88**	.90**	.78**	.94**	.88**	-		
14. LEC Total Potential Trauma	.10	.35**	.35**	.35**	.32**	.20	.38**	.33**	.23	-.04	.20	.30*	.88**	-	
15. Medication Score	.48**	.31**	.45**	.42**	.45**	.42**	.46**	.48**	.45**	.48**	.44**	.27*	.45**	.03	-

Note. * = $p \leq 0.05$, ** = $p \leq 0.01$ Zero-order correlations are reported here for descriptive purposes, corrections for multiple comparisons have not been applied.

2.1.10 Power Calculations to Determine Sample Size

The present study set out to recruit a sample of approximately eighty individuals based on power analyses, time and resources. Categorical analyses were planned to compare three groups of individuals; 1) those with PTSD, 2) those who had experienced a traumatic event but did not meet the criteria for PTSD and 3) a further control group for whom the most stressful event did not meet the Criterion A definition of 'traumatic event'. The statistical power of the test (the probability that it will correctly reject the null hypothesis, see Button et al., 2013) was set at .80. The effect size was estimated based upon a number of studies with comparable hypotheses. A meta-analysis of physiological studies in PTSD by Pole (2007) suggests average effect sizes to be medium (range between r =.08 – r =.34). Cascardi, Armstrong, Chung, and Paré (2015) reported an effect size of (d = 0.79 or f = .40) comparing pupil dilation to threat in individuals with PTSD to controls (a 'large' effect, Cohen, 1988; Selya, Rose, Dierker, Hedeker, & Mermelstein, 2012). Bakes, Bradshaw and Szabadi (1990) did not report effect sizes in their study of anxiety and pupil response, but a computation of Cohen's d from the F-value from the ANOVA reported suggests a large effect size (d = 1.10 or f = .055). G*Power software (Faul, Erdfelder, Lang, & Buchner, 2007) was used to determine an a priori sample size estimate of 42 to detect an effect size at d = 0.79. The sample size for a MANOVA was difficult to determine, as the effect sizes based on previous similar research compared two means. A MANOVA with a medium effect size (f^2(V) = 0.06) required 117 participants for 3 groups with 3 response variables. To detect a large effect size (f^2(V) = 0.16) a sample of 48 would be needed. The dimensional analysis (bivariate correlation) required a sample of 67 to detect a medium effect size (r = .30). A multiple linear regression with one criterion variable (index of performance, e.g. pupillary response) regressed onto the four symptom scale test variables (intrusion, avoidance, negative

alterations in mood and cognition and hyper-arousal) required a sample of 85 to detect a medium effect.

2.1.11 Sample and Exclusions

Individuals were eighty community participants recruited from three third-sector (charity) organisations and one housing association supported accommodation unit. Twenty-eight individuals were recruited from Nottingham, England, from 'Forces in the Community', a charity supporting military service personnel and their families. Twenty-one individuals were recruited from Cardiff, Wales, from both 'The Living Room', a charity supporting individuals with addiction issues, and from 'Ty Seren' a housing project for vulnerable young women. Thirty-one individuals were recruited from Weston-super-Mare, from a homelessness day centre called 'Somewhere to Go'. These organisations were selected due to the likelihood of potentially traumatic life experiences in individuals using these services, whilst avoiding the complication of multiple, high dose medications administered within psychiatric services (see Appendix C for frequencies of medications prescribed within a secure psychiatric sample and Appendix A for the complications arising from psychotropic medication).

Exclusion criteria for the following experimental chapters are based on both a whole assessment basis and on data analysis procedure. Exclusions from data analysis are specific to the experimental paradigm employed and described within experimental chapters. Seven individuals' results were totally excluded due to reasons of ongoing illicit substance abuse (reported use within the last 48 hours) and/or poor compliance with experimental procedure. Ongoing use of substances included heroin, methamphetamine, crack cocaine, cocaine, cannabis, so called 'legal' highs, as well as individuals taking any opiate medication,

including subutex and methadone prescriptions. No individuals that were included reported a history of head injury requiring hospitalisation or diagnosis of traumatic brain injury. All seven total exclusions for reasons of poor participation or illicit substances were from the homelessness day centre and the decision to exclude these individuals' data entirely was made prior to analysis.

2.1.12 General Procedure

The researcher held an information session for staff and volunteers within each organisation, outlined the purpose and procedure of the study, the need for participants to have normal or corrected to normal vision, speak English, be able to read and to be able to tolerate the period of time required for the study session. Potential participants were approached by a member of the staff or volunteer team within the organisation, and either offered an information leaflet or an opportunity to meet with the researcher to ask questions. Participants deemed eligible to take part were reimbursed for their time, which was either cash or as a voucher, at the discretion of the participating organisation. The study payment was not explicitly advertised by recruiting staff to avoid individuals taking part for reasons of monetary reimbursement without considering the information sheet.

The study procedures took place in a private, artificially lit room. Participants were required to complete a check-box style consent form indicating that they understood procedures and had read the dated information sheet, had been given the opportunity to ask questions, understood their rights to withdraw or omit questions, and that they gave their consent to take part. The full study took between two and three hours to complete, depending on whether the CAPS-V interview was indicated. Participants were informed that they could take breaks at any point and were free to pass on questions they did not want to answer.

Participants reported on the demographic features reported in Table 6 below. At the end of the study, participants were fully debriefed, given a debriefing form to take away with them detailing study information and the complaints procedure, and offered an NHS PTSD information sheet. Participants were offered a follow-up 7 days later, but no participants requested this. Participants were offered extra time for the purpose of mood restoration if required. Procedures were designed in line with ethical guidance from the International Society for Traumatic Stress Studies (ISTSS), ethical approval was granted by the School of Psychology, Cardiff University. The standard study procedure is outlined in Table 5. The results of the physiologic measures, Pupillometry 1, Pupillometry 2 and Contrast sensitivity are reported within this thesis.

Table 5. *Standard Order of Procedure for Study Sessions*

1.	Information and informed consent
2.	Demographic information
3.	Contrast sensitivity
4.	Pupillometry 1
5.	STAI and HA Scale
6.	Pupillometry 2
7.	WASI-III
8.	Attention task 1
9.	Attention task 2
10.	LEC-V and Extended Criterion A Assessment
11.	IES-R
12.	CAPS-V interview (if indicated by Criterion A Assessment)
13.	Debrief
14.	Optional consent to follow up after 7 days and anonymous feedback form – RRQ-R

Table 6. *Participant Demographics for the Overall Sample (*N = 73)

Variable		*N*	*M*	*SD*	Range
Age		73	45.32	14.68	18 – 69
Sex	Male	55% (40)			
	Female	45% (33)			
Ethnicity	White British	92% (67)			
	Other	8% (6)			
Education [a]		73	2.73	2.06	0 – 8
IQ		65	104.48	19.26	71 – 139
Psychiatric History[b]		63% (46)			
Previous PTSD assessment		19% (14)			
PTSD/ traumatic stress diagnosis (self-reported)		12% (9)			
PTSD treatment history		6% (4)			
Medication score		73	0.60	0.95	0 – 5
Medication	Physical	25% (18)			
	Mental	21% (15)			
	Both	16% (12)			
	None	38% (28)			
Alcohol use history	None	6% (4)			
	Recreational	60% (44)			
	Heavy	34% (25)			
Substance use history	None	83% (61)			
	Recreational	15% (11)			
	Heavy	1% (1)			
Caffeine (24hrs)		88% (64)			
Nicotine (24hrs)		68% (50)			

Note. Where frequencies are reported under *N*, these are expressed as a percentage, rounded to the nearest whole number. The number in brackets represents frequency total.

[a] Qualifications were coded according to the Regulated Qualifications Framework (England) and the Credit and Qualifications Framework (Wales) (accessed from GOV.UK, 2015)

[b] Self-reported history of any psychiatric diagnosis.

2.1.13 Demographics and Psychometric Results

Demographic information for the whole sample (N = 73) is presented in Table 6. The sample spanned a wide range of ages, was composed of almost equal numbers of males and females, was predominantly white British and of average intelligence. Educational attainment ranged from no completed education to PhD/ DClinPsy/ Medical Doctorate, with average attainment falling somewhere between level 2 (e.g. GCSE grade A* - C) and 3 (e.g. AS/A Level, Baccalaureate, NVQ level 3 or Level 3 Diploma). A prominent feature of this sample is the number of individuals that reported a history of psychiatric disorder. Although based on a self-report estimate, this figure, 63%, is higher than lifetime prevalence estimates for the general population from the National Comorbidity Study and the European Study of the Epidemiology of Mental Disorders (25% life time and 9.6% past 12 months; Alonso et al., 2004; 48% life time and 29.5% past 12 months; Kessler et al., 1994). Within this sample, 12% of individuals self-reported a current diagnosis of PTSD that had been given to them by a professional.

2.1.14 Demographics and Descriptions for Subsections of the Sample

The demographics for the subsections of the sample are reported in Table 7. Figure 1 details the types of traumas reported, following the categories from the LEC.

Table 7. *Participant Demographics for Trauma, Trauma-Exposed Control and No Criterion A Groups*

		PTSD positive (*n* = 23)				PTSD negative (*n* = 32)				Control (*n* = 18)			
Variable		*N* freq	*M*	*SD*	Range	*N*/ freq	*M*	*SD*	Range	*N*/ freq	*M*	*SD*	Range
Age		23	38.59	9.59	21.48 – 58.60	32	43.38	15.42	18.45 – 63.90	18	49.18	13.22	18.62 – 65.84
Gender													
	Male	48% (11)				59% (19)				56% (10)			
	Female	52% (12)				41% (13)				44% (8)			
Ethnicity													
	White British	83% (19)				94% (30)				100% (21)			
	Other	17% (4)				6% (2)							
Education		23	2.57	2.54	0 – 8	32	2.72	1.57	0 – 6	18	2.94	2.24	0 – 8
IQ [a]		20	103	19.80	71 – 138	31	100.32	20.02	72 – 129	19	108.69	22.20	73 – 139
Psychiatric History		91% (21)				53% (17)				45% (8)			
Medication													
	Physical	4% (1)				34% (11)				33% (6)			
	Mental	26% (6)				19% (6)				17% (3)			
	Both	30% (7)				6% (2)				17% (3)			
	None	39% (9)				41% (13)				33% (6)			

Alcohol use history											
	None	0% (0)			13% (4)			0% (0)			
	Recreational	61% (14)			53% (17)			72% (13)			
	Heavy	39% (9)			34% (11)			28% (5)			
Substance use history											
	None	78% (18)			87% (28)			89% (16)			
	Recreational	22% (5)			16% (5)			11% (2)			
	Heavy	0% (0)			0% (0)			0% (0)			
Caffeine (24hrs)		83% (19)			88% (28)			94% (17)			
Nicotine (24hrs)		87% (20)			56% (18)			61% (11)			
IES-R Total			57.70	16.12	28 – 81		16.09	18.15	0 – 64	11.88	20.70	0 – 71
Total Anxiety			97.35	27.61	51 – 146		69.66	23.59	40 – 121	61.41	17.60	40 – 96
Harm Avoidance			25.78	7.50	10 – 35		12.82	8.36	1 – 32	13.67	10.66	0 – 33

Note. Where frequencies are reported under *N*, these are expressed as a percentage, which has been rounded to the nearest whole number. The number in brackets represents frequency total.

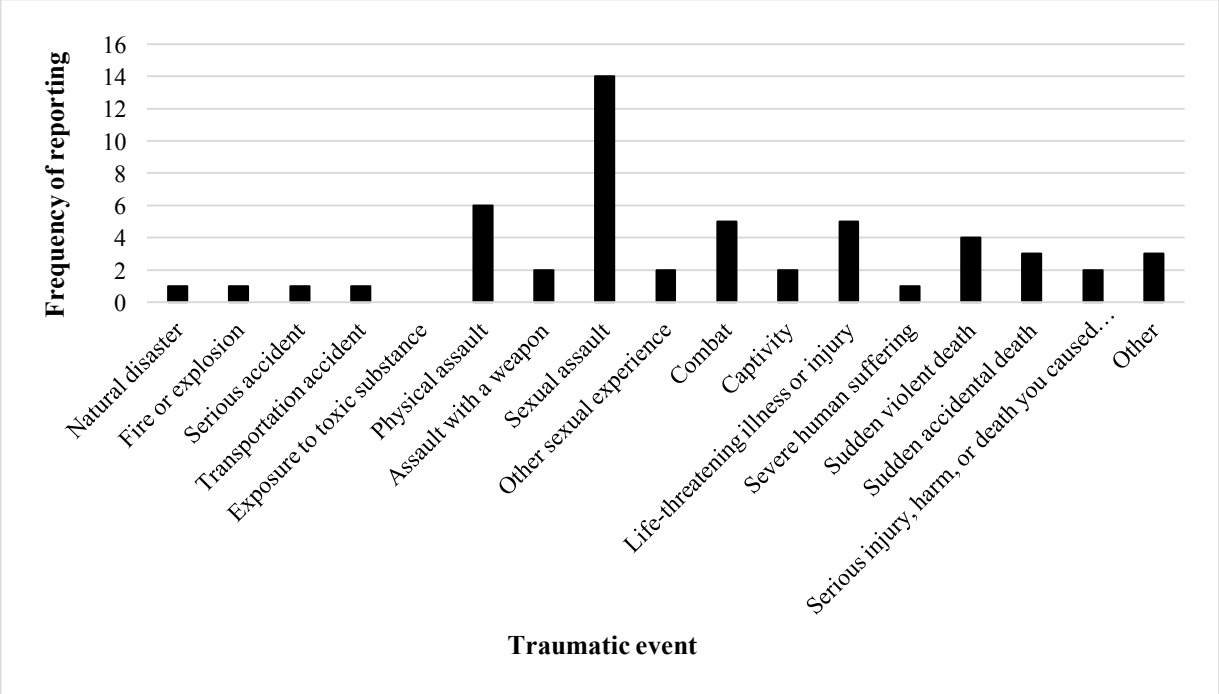

Figure 1. Frequencies of traumatic events experienced within the trauma-exposed sample (*N* = 55).

The sampling was opportunistic and quasi experimental, so an exploration of variation in demographic and potential confounding factors was important. The groups are well matched on education (p = .927), IQ (p = .669) gender, medication rates, histories of alcohol and substance misuse and current caffeine and nicotine use (all X^2 = >.05). Despite equally matched groups, the effect of gender was explored by independent *t*-tests comparing performance outcome measures for males and females. There were no significant results for any measures (all *p*s > .05), suggesting no overall effect of gender on performance. The PTSD positive and negative groups did not differ significantly on age (p = .192), but the control group was significantly older than the PTSD positive group (p = .014). The majority (91%) of the PTSD positive group reported a history of psychiatric diagnosis, suggesting higher psychiatric morbidity in this group. The greater pathology in the PTSD positive group

is also demonstrated by considerably higher levels of both self-reported anxiety and harm avoidance. The PTSD negative and control groups showed comparable levels of psychopathology.

The variation in months since the experience of the Criterion A traumatic event (M = 188.34, SD = 153.64) was large within this sample, with a minimum of 5 weeks and maximum of 516 months. There was a marginally significant negative correlation between symptom severity and time since trauma (r = -.24, p = .077) indicating a trend for a reduction in symptom levels over time. The National Co-Morbidity Study demonstrated that, among individuals with an index trauma, more than one-third fail to recover, even after many years (Kessler et al., 1994) consistent with the finding that many veterans display significant clinical distress years after their return from war (Weiss et al., 1992).

The use of prescription psychotropic medication for mental health was reasonably low in this sample (see Appendix A, Table A20), as compared to previous measures taken from a sample of patients within a low-secure psychiatric hospital (85% prescribed antipsychotic medication [major central nervous system tranquilisers], see Appendix C). Community participants were targeted instead of hospitalised individuals to reduce the complicating effects of large doses of medication and active attempts to medically treat the phenomena being studied.

Table 8. *Trauma Measure Results for PTSD Positive (N = 23) and PTSD Negative (N = 32) Groups*

	PTSD Positive			PTSD Negative		
Variable	*M*	*SD*	Range	*M*	*SD*	Range
Time Since Trauma (months)	157.50	144.31	1 – 408	215.04	153.28	0 – 516
LEC-5						
Total Potential Trauma	11.59*	5.40	3 – 28	8.72	5.04	1 – 23
Number of Index Event Experiences	15.43*	23.45	1 – 100	5.28	10.28	1 – 50
CAPS-V						
Total Severity (max = 80)	42.78**	13.43	19 – 72	7.96	8.88	0 – 31
Total Symptoms (max = 20)	14.09**	3.33	8 – 19	2.47	3.22	0 – 11
Subjective Distress (0 – 4)	2.83**	0.94	1 – 4	0.75	0.92	0 – 3
Impairment in Social Function (0 – 4)	2.87**	0.81	2 – 4	0.46	0.72	0 – 2
Impairment in Occupational Function (0 – 4)	2.78**	1.17	0 – 4	0.26	0.84	0 – 4
CAPS-V Global Severity (0 – 4)	3.17**	0.78	2 – 4	0.66	0.83	0 – 2
IES-R						
Total Severity (max = 88)	57.70**	16.12	28 – 81	16.09	18.15	0 – 64

Note. Maximum scores are indicated for measures. Total potential trauma refers to the number of potentially traumatic experiences indicated from the LEC. Number of index event experiences indicates the amount of times the individual estimated that they had experienced something equally as stressful as the index event i.e. if they had suffered abuse over a prolonged period.
** $p < .05$ ** $p < .001$.

2.1.15 Service Specific Samples

The samples targeted for participation were selected due to their likely exposure to traumatic events. A 25% prevalence of co-morbid PTSD is reported in an inpatient sample of individuals seeking treatment for substance misuse issues by Brown, Recupero and Stout (1995). A further study by Brown, Stout and Mueller (1999) reported that, within an inpatient substance misuse service, half of their sample (n = 48) met DSM-IV criteria for current PTSD. The authors suggested that these individuals apparently overuse costly inpatient addiction services and, despite their higher rates of psychiatric co-morbidity, they did not receive higher levels of support. An estimate of the prevalence of PTSD within general addiction services (as was sampled for this study) was 24% – 27%, lower than the figures reported within specific substance misuse services. Within homeless samples, a study by Taylor and Sharpe assessed 70 homeless men and women and found 98% to have experienced a potentially traumatic event, and the 12-month prevalence of PTSD was 41%. The study suggested that PTSD often preceded the reported trauma, but re-victimisation commonly occurred afterward. Studies of military veterans usually report prevalence of PTSD according to which war or country the veteran served in. Studies of PTSD prevalence in Afghanistan and Iraq veterans vary from 5 – 20 %, but estimates are higher among those seeking treatment (50% positive screening assessments) (Ramchand et al., 2010) A study by Engahl, Dikel, Emberly and Bank (1997) reported that, in prisoners of war (POWs) 53% met criteria for lifetime PTSD, and 29% met criteria for current PTSD. The most severely traumatised group were POWs held by the Japanese, who had lifetime PTSD rates of 84% and current rates of 59%. Estimates also suggest that, of the 1.7 million veterans who experienced symptoms after the Vietnam war, 49% still experienced clinically significant distress, in the absence of a full diagnosis (Weiss et al., 1992).

The samples reported here cannot be said to be representative of the participating populations due to small sample size and non-random sampling. For example, some individuals reported that they sought to take part in the study due to PTSD history and traumatic experiences, which would introduce a bias. However, Table 9 highlights trauma statistics for three of the service specific samples (excluding the women's shelter due to low *N*), and is indicative of high rates of traumatic experiences, PTSD diagnoses, and PTSD symptoms yielding an appropriate sample for the study of trauma.

Table 9. *Comparison of PTSD Diagnostic Status, Symptom Severity Averages and Total Potential Trauma Events Across Service-Specific Samples*

	Military (*n* = 28)	Addiction (*n* = 18)	Homeless (*n* = 25)
	Frequency		
Criterion A Met	68 % (19)	83% (15)	80% (20)
PTSD Diagnostic Criteria Met	32% (6)	53% (9)	36% (9)
	Mean (Standard Deviation), Minimum – Maximum		
Symptom Severity	19.90 (22.40), 0 – 72	26.73 (19.67), 2 – 54	22.7 (21.25), 0 – 57
Total Potential Trauma	8 (5.23), 0 – 22	11 (6.04), 0 – 28	10 (5.60), 3 – 23

Note. Where frequencies are reported, these are expressed as a percentage which has been rounded to the nearest whole number, the number in brackets represents frequency total.

CHAPTER THREE

3.1 Pupillometry and Post-Traumatic Stress Disorder

3.1.1 Abstract

The two studies reported in this chapter investigate the utility of 'cognitive pupillometry' as an assessment method for Post-Traumatic Stress Disorder. Cognitive pupillometry measures fluctuations in pupil size that are linked to internal processes. Here, it has been employed as a measure which is sensitive to changes in arousal levels within the autonomic nervous system, such as occur during emotional arousal and vigilance to threat. In Experiment One, pupil diameter was recorded throughout a passive image viewing task (developed by O'Farell, 2016). In Experiment Two, pupil diameter was recorded throughout a passive listening task (developed by Burley, 2017).

Experiment One assessed indices of resting pupil diameter, an initial constriction reflex and emotional modulation of the pupil within a sample of 65 participants recruited from third-sector military, addiction, homelessness and women's shelter services; 20 met diagnostic criteria for PTSD, 28 had experienced a traumatic event, but did not meet diagnostic criteria and 17 reported an index experience that did not meet the definition of trauma. Participants were assessed using the Clinician Administered PTSD Scale for DSM-V to provide a categorical diagnosis as well as a dimensional symptom severity measure. Pupil activity was recorded during passive viewing of 40 images. Results indicated that pupillometry was sensitive to the emotional content of the stimuli, with differential patterns of pupil dilation observed during viewing of positive, negative-threat, negative-distress and neutral images. Consistent with the hypotheses, there was no evidence for alterations in resting pupil

diameter in individuals with PTSD. Individuals with PTSD differed to both control groups in showing a reduced initial constriction response and a higher level of emotional modulation to fear and happy images.

Experiment Two assessed indices of resting pupil diameter and emotional modulation of the pupil during passive listening of 30 sound clips. Results indicated that pupillometry was sensitive to the emotional content of the stimuli for unpleasant sounds. Again, there was no evidence for alterations in resting pupil size. Contrary to the findings of Experiment One and hypotheses, the emotional modulation to sound clips did not differ according to PTSD status.

Experiment One supported a previous application of pupillometry to the study of PTSD (Cascardi et al. 2015), extended the assessment to additional stimulus categories, and described the entire waveform of the pupil response, revealing differences in the initial constriction reflex. This finding is in line with the PTSD literature suggesting hyper-vigilance to threat, but poor regulation of the parasympathetic branch of the autonomic nervous system, which has been linked to adverse health outcomes and cardiovascular problems in PTSD. Experiment Two, using an alternate form of stimuli, did not replicate this finding. It is suggested that the lack of an effect in experiment two is due to differences between the paradigms, such as internal reliability. Individuals with PTSD also showed reduced pupil constriction after image onset and enhanced emotional reactivity. The effect sizes for these differences were large. Dimensional analyses suggested higher levels of PTSD symptom severity were associated with increased emotional modulation, but with weaker effect sizes. Overall, the results from this chapter support the use of different indices of pupil function and emotive images in the assessment of PTSD.

3.1.2 Introduction

3.1.2.1 Pupil Dilation and Cognitive Pupillometry

Changes in the size of the pupil primarily reflect changes in the light level of the external environment, but can also provide a window to the activity of the internal environment via the autonomic nervous system (ANS). Studies utilising the size of the pupil as an indicator of ANS activity date back to the 18th Century (du Petit, 1727, see Lowenstein & Loewenfeld, 1958), but exploration outside of the identification of physical illness was limited by the painstaking methods applied, including pupil photography and manual measurement. Advances in technology, such as the instrument developed and reported by Lowenstein and Loewenfeld (1958), enabled methods of pupillary measurement to become more widely used for research purposes outside of ophthalmologic or medical examination, and enhanced the temporal resolution of these methods. The pupil has been recognised as an indicator of interest for thousands of years. Historic accounts suggest use of *Atropa belladonna* by Egyptians to dilate the pupil for cosmetic purposes (see Duncan & Collison, 2003) and by European women during the Middle Ages to make their eyes look 'more attractive' (Dundes, 1981). Recent evidence supports this idea, in that faces with dilated pupils are considered more attractive (Tombs & Silverman, 2004) as they are indicative of sexual interest. The use of 'cognitive pupillometry' (Beatty & Lucero-Wagoner, 2000) is the assessment of change in pupil diameter during varying psychological states, such as interest, which enables research to progress further than assessing the communicative impact of pupil dilation. In psychology, the use of cognitive pupillometry was first reported in a seminal study by Hess and Polt (1960), who reported fluctuations in pupil size due to emotional tone and arousal. This method attracted interest as a basis for the objective measurement of internal states such as emotion, interest, lie detection, and for use within assessment and

marketing. Dilation of the pupil has since been used as an index of active processing and mental effort (Hess & Polt, 1964; Kahneman & Beatty, 1966); emotional processing (Partala & Surakka, 2003; Granholm & Steinhauer, 2004; Bradley, Miccoli, Escrig, & Lang, 2008), and to assess individual differences in traits and symptoms associated with mental illness and disorder (Burkhouse, Siegle, Woody, Kudinova, & Gibb, 2015; Cascardi, Armstrong, Chung, & Paré, 2015; O'Farrell, 2016; Burley, Gray, & Snowden, 2017).

The diameter of the pupil in adults varies from 2 - 4 mm in bright light and from 4 - 8mm in the dark (Spector, 1990). Pupil diameter is determined largely by the light reflex, to control the light entering the eye, and the accommodation reflex, to control the focus of the lens (Beatty & Lucero-Wagoner, 2000). The mechanism of control is comprised of opposing contractions of two muscles within the iris, the sphincter (constrictor) pupillae and the dilator pupillae. Pupil dilation can be caused by both an increase of activity in the sympathetic nervous system, innervating the dilator muscle, or by inhibition of parasympathetic innervation to the sphincter muscle (Steinhauer, Siegle, Condray, & Pless, 2004). In addition to large-scale reflexive changes in diameter, the sphincter and dilator muscles also produce constant, visually insignificant fluctuations, appearing to serve no functional purpose (i.e., do not produce a perceptual change). These small fluctuations, the largest of which would be around 0.5 mm, are considered a by-product of SNS and PNS activity and have been the focus of cognitive pupillometry (Beatty & Lucero-Wagoner, 2000).

Within cognitive pupillometry, Steinhauer et al. (2004) examined the contributions of the SNS and PNS pathways to pupil dilation. The authors found pupil dilation in participants completing a difficult task (subtract 7 from a digit), and suggested the mechanism for this was parasympathetic inhibition during sustained attention. The authors isolated the

autonomic mechanism by using pharmacological blockade (blocking of the parasympathetic sphincter muscle versus blocking of the sympathetic dilator muscle). They found increased pupil dilation in all conditions, and, importantly, sustained pupil dilation when PNS activity was intact. Bradley et al. (2008) also employed a cognitive pupillometry paradigm to monitor pupil changes to affective images whilst measuring autonomic activity (skin conductance as an indicator of SNS function and heart rate deceleration as a measure of PNS function, [see Berntson, Boysen, Bauer & Torello, 1989]). The authors found skin conductance responses co-varied with pupil change during picture viewing, and suggest that the mechanism behind pupillary change during affective picture viewing is emotional arousal associated an increase in SNS activity.

3.1.2.2 The Pupil Light Reflex in Cognitive Pupillometry

The pupillary light reflex (PLR) occurs in response to light, and is assessed experimentally by delivering a flash of light to a dark adapted pupil (e.g., 200 ms flash of collimated white light; Heller, Perry, Jewett, & Levine, 1990, or presentation of a green light-emitting diode; Bakes, Bradshaw, & Szabadi, 1990) whilst measuring pupil activity. The autonomic component of the PLR after dark adaption depends on parasympathetic outflow from the Erdinger-Westphal (E-W) nucleus (see Lowenstein & Loewenfeld, 1969). Heller et al. (1990) investigated the autonomic components of the reflex using pharmacological blockade, and suggest that cholinergic inhibition of the dilator muscle contributes to the constriction of the pupil. Within cognitive pupillometry, a reduction in the light reflex has been observed during experimental paradigms manipulating mental and emotional processing (Steinhauer, Condray, & Pless, 2015). Steinhauer and colleagues used a demanding cognitive

task (subtract 7 from a digit) to demonstrate attenuation of the light reflex during mental effort, and investigated the mechanism of attenuation by blockade of the pupillary dilator muscle. The authors suggest that the primary pathway for reduction in the light reflex was mediated by the PNS.

Attenuation of the light reflex has been shown to be produced by emotional arousal, including anticipation of aversive stimuli such as electric shock (Bitsios, Szabadi, & Bradshaw, 1996). Modulation of the initial light reflex can also be experimentally induced by passive viewing of pictures, with both negatively (violence) and positively arousing (erotica) pictures producing a reduction in the reflex (Bradley et al., 2008; Henderson, Bradley, & Lang, 2014). Within quasi experimental paradigms the light reflex has been shown to be reduced in individuals with anxiety disorder relative to controls (Bakes et al., 1990) and reductions in light reflex have been used as indicators of autonomic dysregulation in patients with schizophrenia (Bär et al., 2008). The latter findings are important for the present research as it demonstrates that the PLR can be used as a valid measure of a diagnostic construct.

3.1.2.3 Post-Traumatic Stress Disorder and Autonomic Arousal

Since introduction to the Diagnostic and Statistical Manual (DSM-III; American Psychiatric Association, 1980) a diagnosis of Post-Traumatic Stress Disorder (PTSD) has included symptoms of excessive autonomic arousal. The first laboratory based study of trauma symptoms and physiology pre-dated standard diagnostic structure and assessed Heart Rate (HR), Respiratory Rate (RR), Galvanic Skin Response (GSR), and Electromyography (EMG) (Dobbs & Wilson, 1960). This study provided evidence for increases in these

parameters in individuals with persistent 'war neurosis'. After the addition of the post-traumatic stress diagnosis to the official nosology, further laboratory studies replicated these psychophysiological results, suggesting increased baseline autonomic arousal (Blanchard, Kolb, Pallmeyer, & Gerardi, 1982; Fairbank, Keane, & Malloy, 1983; Pitman, 1989). A meta-analysis of physiological studies in PTSD, which included studies of resting baseline arousal, startle paradigms, and those using idiographic trauma cues found consistent support for elevated psychophysiological responses (Pole, 2007). However, most early studies are constrained by the population studied, with a disproportionate focus on male veterans of war. Studies have employed animal models to demonstrate persistent physiological abnormality after juvenile trauma in mice (e.g. Cohen et al., 2007); and this has also been shown in human children (see Perry, 1994 for a review). Furthermore, a theory of underactivity in the PNS and relative over activity in the SNS has been proposed by Streeter, Gerbarg, Saper Ciraluo and Brown (2012) to explain a potential mechanism behind beneficial effects of yoga practice within stress-related disorders, including PTSD. To further support the hypothesis of disrupted PNS activity in PTSD, Agorastos et al. (2013) found blunted tonic parasympathetic activity, which altered heart rate dynamics in male veterans with PTSD. The authors suggest that the apparent autonomic imbalance in PTSD conveys a risk for increased cardiovascular disease in PTSD.

Zoldaz and Diamond (2013) reviewed the research into the stereotypic physiological abnormalities in PTSD, and suggest the factors associated with the expression of PTSD are more complex than are commonly described. As discussed in Chapter One, efforts to describe PTSD as a homogenous construct are confounded by inconsistency of expression, and influenced by many factors including; early life stress, previous trauma, sex, age, and psychosocial factors including personal support and cognitive appraisal. The authors suggest

there is great challenge in developing behavioural and biomarker based assessment and diagnostic tools for use within PTSD.

3.1.2.4 Cognitive Pupillometry and Post-Traumatic Stress Disorder

The use of pupillometry to assess autonomic function in PTSD is reasonably new and infrequently studied. To date, there are four published studies in this area, the first three assessed eye tracking and pupil response, whereas the most recent is exclusively focussed on the pupil response. Kimble, Fleming, Bandy, Kim and Zambetti (2010) recruited nineteen veterans and used a median split to assign these individuals to PTSD high and low groups. Veterans viewed a split screen display consisting of a trauma-relevant image of war versus a neutral image, or negatively valenced images versus neutral images. Participants in the high-PTSD group demonstrated larger pupils to all negatively valenced images. Felmingham, Rennie, Manor and Bryant (2011) recruited twenty-one traumatised participants to assess physiological reactivity to one second displays of four threatening words or neutral words. Individuals with PTSD (n = 11) had larger pupils when viewing both neutral and trauma relevant words, but there were no group differences in baseline pupil areas. This suggests that these individuals showed higher arousal while processing images, rather than threat specific arousal, and may have been an effect of effort employed during the task. Kimble et al. (2014) manipulated hypervigilance via task instruction. The assigned undergraduate participants (N = 70) to one of three conditions; hypervigilance (n = 25), pleasant control (n = 24) and control (n = 21). Participants in the hypervigilant group were asked to look for a threatening target to avoid intermittent noise bursts (noise bursts were random and unrelated to performance), and assessed self-reported anxiety, scan paths, and pupil size whilst looking at

a series of neutral scenes for 10 seconds each. They reported significantly larger pupil dilations to neutral scenes in hypervigilant conditions, relative to control conditions, suggesting increased arousal and mimicking the hyper-vigilance symptoms of PTSD.

The first and only study assessing whether pupillometry could serve as a diagnostic measure (as opposed to eye tracking or non-diagnostic group comparison approaches discussed above) was reported by Cascardi, Armstrong, Chung and Paré (2015). The authors assessed the hypothesis that arousal-related pupil response would be differentially expressed in trauma exposed individuals with and without a DSM-IV diagnosis of PTSD. They also assessed the diagnostic accuracy of their model. The sample was made up of forty individuals, sixteen of whom met diagnostic criteria for PTSD. The task used three 'threatening' images from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1997) consisting of a figure in a balaclava, a hand wielding a knife and a man pointing a gun at another man's head. These three images were carefully matched to three 'neutral' pairs on dimensions of luminance, number, location and size of figural components, and the ethnicity of protagonists. Respondents were instructed to visually explore the images however they wished. Pictures were displayed for 30 seconds, and fixations on the threatening areas of the image were extracted. Pupil size was assessed within these extracted areas of interest. Hierarchical logistic regressions assessing contributions of anxiety, time since trauma and PTSD diagnostic status suggested that the larger pupil dilations within the areas of interest uniquely accounted for 12% of the variance in PTSD diagnostic status. The final model accounted for 85% of the variance in PTSD status and correctly classified 93.8% of individuals. The authors conclude that pupil reactivity to threatening images shows promise as a physiological marker for PTSD.

Consistent with the diagnostic features of PTSD (persistent negative emotional state and persistent inability to feel positive emotions; Criterion D, items 4 and 7) individuals often report intense negative emotion, whilst being unable to elicit and express emotion in other situations (Horowitz, 1986; Litz et al., 2000) (see section 1.1.3 for a review of emotional processing theories in PTSD). No studies to date have assessed pupil reactivity to positive imagery in PTSD, despite a literature evidencing alterations in arousal to positive stimuli.

Despite much anecdotal evidence to suggest PTSD is associated with increased resting pupil dilation, there is a paucity of research evidence. Although the tonic autonomic imbalance suggested to be present in PTSD (Agorastos et al., 2012) indicates a chronic state, at present, there is no research evidence to suggest resting pupil size is sensitive to this imbalance. Contrary to the hypothesis of larger resting pupil size, the only study to isolate resting pupil diameter as a parameter in PTSD studies (Felmingham et al., 2011) reported no group differences. The studies of Kimble et al. (2010), Felmingham et al. (2011) and Kimble et al. (2014) suggest that the hypothesised hyper-arousal due to PTSD symptomology has impacts on pupil dilation during processing of both trauma-specific and generally aversive conditions and, moreover, hyper-arousal can also impact on pupil dilation to neutral stimuli. The meta-analysis by Pole (2007) reports that heart rate and galvanic skin response parameters are sensitive to baseline increases in arousal, but the effect sizes were much lower than studies employing standardised trauma cues or ideographic cues. As the conditions within the pupil tasks reviewed all require some element of processing, it is possible that the baseline, resting pupil diameter is not sensitive to arousal in PTSD, only the modulated reactions are detectable. Within other areas of literature, Davis, Daluwatte, Colona and Yao (2013) demonstrate increased pupil diameter during both arithmetic tasks and submersion of an arm in cold water (a ‘cold pressor test’ to stimulate the SNS). However, the results of this

arousal were not sustained after the task. Within studies of the PLR and anxiety, Bakes et al. (1990) also reported no group differences in resting pupil diameter, although they reported a robust reduction in the PLR for anxious individuals. The review of evidence does not suggest that baseline pupil size would be associated with PTSD symptom severity, but it is difficult to make a firm conclusion due to lack of evidence.

The study by Cascardi and colleagues (2015) deviates from the other literature focussing on PTSD and pupil reactions and suggests that the pupil of those with PTSD was uniquely sensitive to threat-specific arousal. However, the study did not include any comparison negative or positive images. The authors' study differs significantly from the others in several ways. Firstly, the images were displayed for 30 seconds, significantly longer than other paradigms, and data was only analysed in regions of interest, when fixations to specific threat elements were apparent. The data for the entire viewing period revealed no within group differences between neutral and threat dilation, nor any significant differences between PTSD and non-PTSD groups. The authors also recruited individuals with specific violent victimisation experiences, thus the threat images displayed could also be considered trauma-specific. The authors' results do not include a positive arousal control condition, or any description of the emotionally modulated light reflex and no differences in initial or overall pupil dilation are apparent. The predictive ability of the final model, which explained an impressive 85% of the variation in PTSD, is also largely determined by anxiety scores, with pupillary variation accounting for 12% of the unique variance. The authors' choice of PTSD status as a dependent (criterion) variable within hierarchical regression models was essential to meet the aims of the study, to use pupillary reactions to predict PTSD diagnostic status. However, the unique ability of diagnostic status in predicting pupillary reaction cannot be explored with a logistic regression and is not discussed.

3.2 Experiment One: Pupillometry to Affective Images

The study outlined below aimed to assess differences in pupillary response according to PTSD diagnostic status, and assess the relationship between PTSD symptom severity and indices of pupillary function using a passive image viewing paradigm (developed by O'Farell, 2016). Images with negative-threat, negative-distress, positive, and neutral content were displayed to assess whether arousal associated with PTSD symptoms is threat-specific, to provide measures of resting pupil diameter, and to describe the initial constriction response to light on image onset. The latter aim, to assess relationships between pupillary constriction and PTSD symptom severity, has not been reported in a trauma population prior to this study.

3.2.1 Hypotheses

Based on a review of the literature relating to three indices of pupillary function it is hypothesised that individuals with PTSD;

1. Will not differ from controls in their level of initial pupil dilation. There will be no relationship between initial pupil diameter and symptom severity.
2. Will have a reduced initial reflexive constriction (ICR) reaction of the pupil during image onset. Higher levels of PTSD symptom severity would be related to a reduction in the ICR. This will be tested by examination of ICR to the neutral stimuli where no modulation due to affective content is expected.
3. Will show greater emotional modulation of the pupil to negative-threat images. This will be indexed by the difference between the pupil size to the threat (fear) stimuli and the neutral stimuli during re-dilation the later time window (1000 – 2000 ms) after the ICR. Higher levels of PTSD symptom severity would be

related to emotional modulation dilation during viewing of threat images as compared to neutral images.

Exploratory analyses will be performed to assess emotional modulation for positive and distress images.

3.2.2 Method

3.2.2.1 Sample and exclusions

The full sample was made up of eighty individuals, full details of which can be found in Chapter 2, section 2.1.13. During data analysis, five individuals were excluded due to >50% missing data within analysis windows. Extreme outlying values distorting normality were identified with histograms, extreme value outputs, Shapiro-Wilk tests, and box and whisker plots. One individual was excluded due to multivariate outliers in data (Mahalanobis distance = 25, $df = 3$), two individuals were excluded due to extreme univariate outliers in two outcome variables. The final sample of sixty-five contained forty-eight individuals who had been exposed to a Criterion A traumatic event, twenty of whom met diagnostic criteria ("PTSD positive" group) and twenty-eight did not ("PTSD negative" group). There were seventeen participants for whom the most stressful thing they had experienced did not met the Criterion A definition of a traumatic event ("control" group). Psychometric properties are reported in Chapter 2, sections 2.1.3 - 2.1.7 and key demographic variables are presented in Table 10 below.

Table 10. *Age, Gender and IQ Demographics for Experiment One*

	PTSD Positive (*n* = 20)	PTSD Negative (*n* = 28)	Control (*n* = 17)	Internal consistency
Age	38.25 (*10.26)*	45.24 *(15.42)*	50.27 *(12.76)*	
Gender	50% female	43% female	47% female	
IQ	103.59 *(20.28)*	104.76 *(16.57)*	109.47 *(22.75)*	
CAPS-V	41.90 *(14.12)*	8.54 *(9.25)*	-	.95
IES-R	55.60 *(15.76)*	18.12 *(18.51)*	9.87 *(19.61)*	.97

Note. Mean *(Standard deviation)*. Internal consistency assessed through Cronbach's alpha.

3.2.2.2 Materials

The psychometric and assessment measures used are reported in Chapter 2, section 2.1.2. The experimental paradigm employed was developed by O'Farrell (2016) and full details of task piloting, development, and use in a forensic sample are reported within the thesis. Results for emotional modulation by threat ('fear') images are reported in Snowden et al. (2016).

The task was a passive image viewing paradigm, made up of 40 images selected from the IAPS[1]. The IAPS contains emotional scenes, which were divided into four emotive categories and presented in a pseudo-random order. Negative-threat ('fear') images were selected from the affected category identified by Barke, Stahl, and Kroener-Herwig (2012). Negative-distress ('sad') images and positive-adrenaline ('happy') and neutral images formed

[1] IAPS reference numbers of stimuli used: Fear: 1220, 1300, 1301, 1321, 1930, 1932, 6250, 6300, 6370, 9405; Sad: 2800, 3230, 3350, 2730, 2710, 3180, 9040, 9410, 9250, 3266; Happy: 8501, 8161, 2216, 8034, 8200, 8350, 2208, 4599, 8470, 8490; Neutral: 7002, 7004, 7006, 7009, 7010, 7020, 7025, 7030, 7031, 7150.

the remaining categories. Fear, sad and happy images were rated on a 10-point scale by participants during task development by O'Farrell (2016). Images were matched on dimensions of emotion as well as figural components and complexity. The emotional matching was conducted based on IAPS manual ratings. IAPS manual ratings are made on the dimensions of arousal and valence, obtained in norming studies (Lang et al., 1997). Arousal reflects the intensity of motivation system activation; from calm to high activation, and valence represents the attractiveness or averseness of the stimulus (Lang et al., 2008). Images were also matched on 'complexity' by participant rating and, during task development, the number of figural components were also matched, for example, the number of people (figures) in the foreground.

For each image, the affective/neutral categorisation determined which stimuli were deemed exemplars of affective categories. For example, if a stimulus had a mean happy rating of 7, a mean sad rating of 1.5, a mean fear rating of 1, and a mean neutral rating of 3, that image was considered to represent a happy image. Based on these pilot ratings, 10 images per stimulus type were selected.

The fear image set contained pictures representing threat. Both animals and humans were used in the stimulus set, for example, tooth baring animals (shark, bear and dog), and humans bearing weapons (gun and knife) and wearing balaclavas. The sad image set contained distressed humans, for example crying children, starvation and bruised/injured people. The happy stimulus set contained images of humans and animals being playful, for example playing puppies, marriage, winning sports contests, and non-erotic romance. The neutral category contained humans and scenes, for example a woman on a phone, a man looking at a computer and images of transport and objects (bus, car, spoon and fan).

As reported in Snowden et al. (2016), images were converted to greyscale and matched on dimensions of image contrast and luminance using Adobe Photoshop Elements 12.0 (see also Bradley, Sapigao, & Lang, 2017 for the importance of contrast and luminance matching). Image dimensions were 1920 x 1080 pixels, filling the 17-inch screen. Each test image was preceded by a grey screen presented for 3000 ms. This blank screen included a fixation mark for the first 1000 ms. The same blank screen was presented for 5000 ms following the stimulus to allow the pupil to return to baseline.

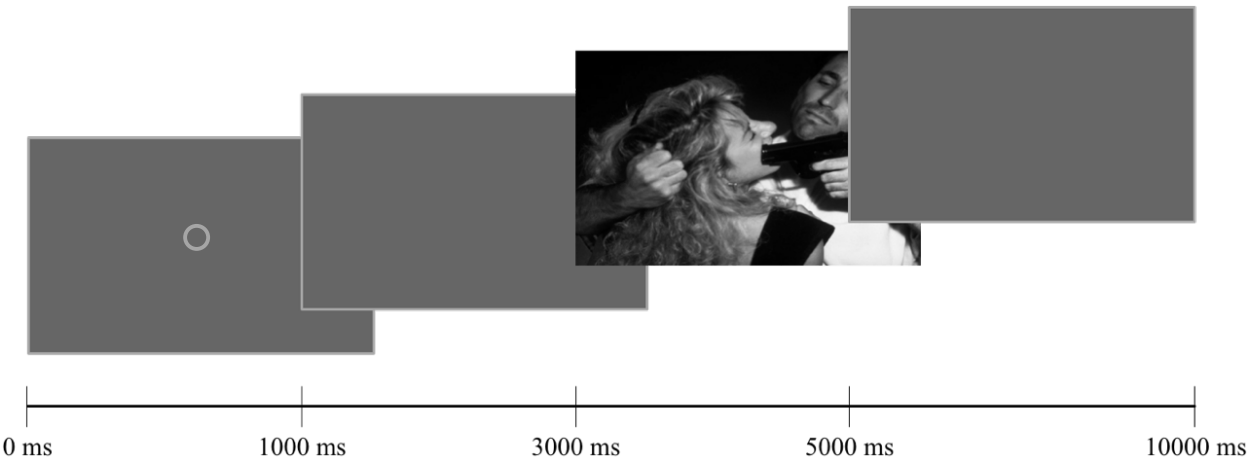

Figure 2. A visual representation of an experimental trial.

3.2.2.3 Procedure

The general study procedure can be found in Chapter 2, section 2.1.12. A participant was seated approximately 60 cm away from a laptop screen, underneath which a Tobii-X260 eye tracking device was secured. A calibration procedure was conducted for each participant using a 5-point calibration screen. During calibration, the participant was instructed to view a moving target (red dot) as it moved sequentially between 5 points over the course of 10 seconds. The eye tracker then located the participant's pupils within an area of three-

dimensional space, allowing for small head movements to occur without interrupting measurement, and negating the need for a head rest. Participants were informed that a series of images would be displayed in greyscale in the centre of the screen. Participants were informed that they were free to look at any aspect of the images, but should not take their eyes away from the screen at any point. Participants were informed that the task would take roughly five minutes, asked to pay attention throughout, and advised that they could blink during the task.

3.2.2.4 Presentation Hardware and software

Stimuli were presented using E-Prime Professional software and pupil diameter was assessed by the Tobii X2-60 Hz eye system. All stimuli were presented in the centre of the monitor, against the light grey background of a Toshiba TECRA W50- A-102 laptop with a 17-inch screen and 60 Hz refresh rate.

3.2.2.5 Data Cleaning and Reduction

The data cleaning methods are identical to that of Snowden et al. (2016) (also reported in; O'Farrell, 2016; Burley, Snowden & Gray 2017). The diameters of the left and right pupils were recorded once every 16.67 ms across trials for each condition. An average of the two eyes is reported in millimetres, where data is missing for one eye the monocular estimate is taken. Any pupil constriction or dilation greater than 0.38 mm within a 16.67 ms interval was attributed to random fluctuation, sometimes occurring around blinks, and was removed (consistent with Partala & Surakka, 2003). Data within 33.34 ms around these points were also removed to avoid anomalous readings. Missing data figures are reported after cleaning. A pre-stimulus onset 'baseline' period of 200 ms (Leknes et al., 2013) was calculated for each trial and subtracted from each subsequent data recording to establish a

change score metric. This 200 ms baseline was averaged across trials to produce an initial pupil diameter. Graphs are displayed using running median smoothing for ease of visual representation, but data used for the analysis did not use this smoothing. The analysis was conducted using a purpose written script in Python using NumPy and Pandas extensions (see Appendix D).

3.2.3 Results

3.2.3.1 Order of Analyses

Analysis of initial pupil dilation (IPD; 200 ms prior to stimulus onset) is conducted first, followed by the initial constriction response (ICR; 500 – 1000 ms post stimulus onset), followed by the emotional modulation (1000 – 2000 ms post stimulus onset).

Figure **3** illustrates these analysis windows for the full sample, and figures 4 – 6 illustrate the full waveform by group.

The rationale for the three time windows representing the IPD, the ICR and emotional modulation were based on previous research (Burley, 2016; Burley et al., 2017; O'Farrell, 2016; Snowden et al., 2016) and the need to create a short, simple task which could be administered and tolerated in a clinical sample. The IPD was represented by the 200 ms resting baseline period, based on previous research (Leknes, 2013; Snowden et al., 2013). Research into the PLR suggests that latency and amplitude of the reflex can be influenced by stimulus intensity and varies between individuals (Ellis, 1981), so, rather than a shorter period, a 500 ms window was chosen to represent some potential variation between stimuli and individuals. Ellis (1981) demonstrated that the minimum latency of the PLR was around

220 ms in humans, and the preparatory work of O'Farrell demonstrated that this time window captured both the onset of the ICR and most of the maximal constriction amplitude prior to re-dilation for this stimulus set. The 1000 – 2000 ms period contains the point at which maximal dilation occurs (Partala & Surakka, 2003; Snowden et al., 2016). This period is also the earliest time point at which emotional modulation appears, capturing automatic appetitive and defensive reactions, and This window was chosen during task development by O'Farrell (2016), and necessarily maintained as the reliability of the pupil indices is poor after image offset and the initial 0 – 1000 ms recording largely represents the period of the ICR (see

Figure **3**).

3.2.3.2 Covariates

The groups were not equally matched on age (see section 2.1.14) as the control group who did not report a Criterion A traumatic event was significantly older and, although not statistically different, the trend suggests that the PTSD positive group is the younger group. Therefore, the potentially confounding effects of age have been considered and relationships between age and pupillary outcome variables are shown in Table 11. Results indicate a significant negative relationship between age and the outcome variables of IPD and emotional modulation to happy images. O'Farrell (2016) reports a significant negative relationship between age and emotional modulation by happy images. Consistent with this, there were negative trends between age and emotional modulation to happy, fear and sad images within this study, suggesting a reduction in emotional arousal, which has also been demonstrated within the literature (Levenson, Carstensen, Friesen, & Ekman, 1991; Pfeifer et al., 1983; Smith, Hillman, & Duley, 2005; Tsai, Levenson, & Carstensen, 2000). Existing studies have attributed this to an effect of reduced autonomic reactivity, rather than subjective

experience, within old age[2]. ANCOVA and MANCOVA have been used throughout to control for the potential effects of age. The pattern of statistical effects with controls for age is a more conservative measure, but results reported below were not changed during replication of analyses without this control measure.

3.2.3.3 Statistical Analyses

The methods of analysis involved both categorical (PTSD diagnostic status) and dimensional (PTSD symptom severity) statistical tests. Categorical analyses included three groups of participants; individuals who met criteria for a diagnosis of PTSD ('PTSD positive'), determined by the CAPS-V, individuals who had been exposed to a traumatic event but did not meet criteria for a PTSD diagnosis ('PTSD negative'), and individuals who did not report any traumatic experience ('control'). Statistical tests were assessed for violations in assumptions, and removal of participants due to violations (n = 3) are detailed in section 3.2.2.1[3]. Although extreme outlier values were removed for individuals classified as extreme across multiple variables, the variable for the emotional modulation by happy images remained in violation of normality and normality of residuals as determined by Shapiro-Wilk tests. Histograms suggested that normality was acceptable in adherence to a bell-shaped curve. Statistical literature generally suggests that ANOVA designs are robust to violations in normality (Schmider, Ziegler, Danay, Beyer, & Bühner, 2010). Homogeneity of regression slopes were assessed as nonsignificant through the interaction terms, multivariate outliers

[2] Note. The participants in these studies were considered 'elderly' and over the age of 70. It is possible that there was not enough power in this study to detect a statistically significant effect of age, but, as there are no current studies of pupil response to emotion in old age it may be useful to follow this up in an older sample, with less pathology.

[3] Analyses re-run including statistical outliers did not affect the pattern of significance

through Mahalanobis distance, homoscedasticity of standard residuals through plots, homogeneity through Levene's test, and homogeneity of covariance matrices through Box's M. Regression analyses also included analyses of VIF factors to assess for multicollinearity or redundancy of variables in the model, which were all below 3.5, and considered acceptable (O'brien, 2007). Planned comparisons were conducted per hypotheses comparing the PTSD positive group to those without a diagnosis, with Bonferroni corrections as footnotes. Effect sizes are reported for each significant difference.

Dimensional analyses were necessarily only conducted in the PTSD positive and PTSD negative sample ('trauma exposed group'), as individuals who did not meet the specifications for a Criterion A definition of 'traumatic event' were not given a CAPS score. Analyses included both zero-order correlations to assess relationships between PTSD total severity, and linear multiple regression to assess unique contributions of symptom subscales. In the regressions, the criterion variable is always a performance measure of pupillary function including IPD, ICR and emotional modulation during re-dilation. The test variables were the four subscales from the CAPS-V (intrusion, avoidance, negative alterations in mood and cognition and hyper-arousal).

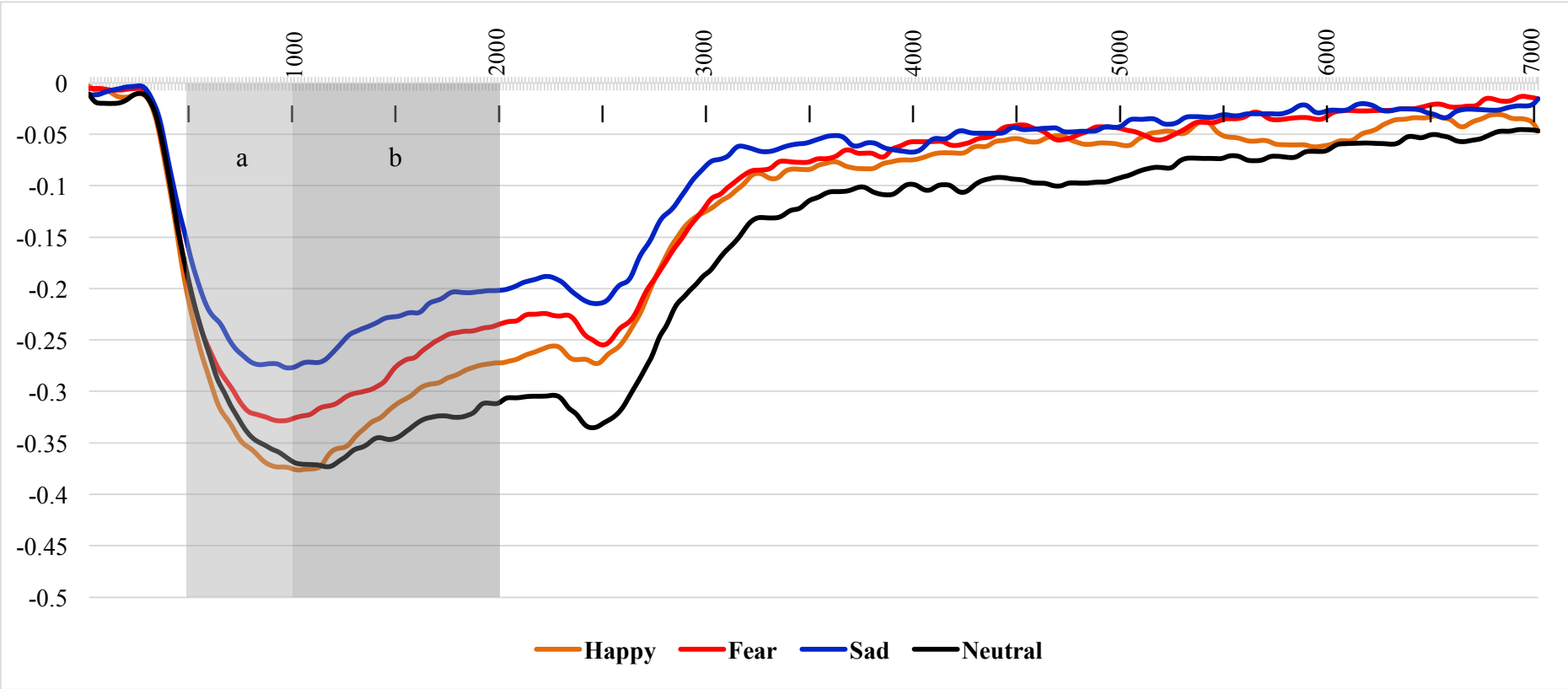

Figure 3. Mean change in pupil diameter from stimulus onset at 0 ms to 7000 ms for $N = 65$ participants. Stimulus offset occurred at 2000 ms. The shaded areas represent the two analysis windows of interest. a = 500 ms – 1000 ms: the initial constriction response, and b = 1000 ms – 2000 ms: the re-dilation response.

3.2.4 Initial Pupil Diameter

3.2.4.1 Missing data

Total missing data within this window, after data cleaning, was 14.16%.

3.2.4.2 Reliability

Reliability was assessed through a split half measure. Experimental trials were divided into 'odd' and 'even' between which the mean pupil diameter for the analysis window were compared. Correlational reliability analysis (corrected by Spearman-Brown; $2r / 1+r$) suggested almost perfect reliability for initial pupil diameter ($r = .99$).

3.2.4.3 Categorical Group Differences in the Initial Pupil Dilation

An ANCOVA was used to determine the effect of PTSD status on IPD, controlling for age. After adjustment for a significant effect of age ($p < .0005$), there was no significant difference in IPD across groups, suggesting no differences in the IPD were attributable to PTSD status between the PTSD positive ($M = 3.68$, $SD = 0.80$), PTSD negative ($M = 4.08$, $SD = 0.75$) and control ($M = 4.07$, $SD = 0.76$) groups $F(2, 61) = 1.76$, $p = .181$. Pupil sizes in the full sample varied from 2.45 – 6.15 mm, which is within the normal range (2 - 9 mm; Winn, Whitaker, Elliott, & Phillips, 1994; 2 - 8 mm; Spector, 1990).

3.2.4.4 Dimensional Analysis of Initial Pupil Dilation

Analysis of zero-order correlations (Table 11) indicates that IPD was not significantly associated with any outcome variables, but was highly related to indices of initial pupil

constriction and was also negatively associated with age. The negative relationship between the ICR and IPD indicates that the greater the initial pupil size, the greater the pupil constriction response (a negative correlation as a greater constriction is represented by a lower negative value). The finding that the IPD was not related to PTSD symptom severity as assessed by either the CAPS-V or the IES-R was important and suggested that individuals with higher symptom severity did not demonstrate abnormality in resting pupil size. As has been found in previous work (Winn et al., 1994) the IPD was also significantly associated with age, which has been included as a covariate throughout.

To assess whether any of the PTSD subscales were uniquely related to the IPD, a multiple regression was conducted. PTSD symptom severity scales using the CAPS-V were the test variables, and IPD the criterion. Inter-correlations are reported in Table 11 and regression statistics in Table 12. Regression analysis indicated that none of the symptom severity scores were uniquely predictive.

Table 11. *Zero-order Correlations Between PTSD Severity, Total Anxiety, Medication and Pupil Responses within the sample (N = 65 for measures not using the CAPS, n = 48 for CAPS measures)*

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1. Total Anxiety	-												
2. Medication	.55**	-											
3. CAPS-V	.68**	.39**	-										
4. IES-R	.69**	.36*	.88**	-									
5. IPD	.12	.06	.03	-.15	-								
6. ICR Neutral	.25*	.14	.35**	.26*	-.58**	-							
7. EM Fear	.19	.12	.29*	.15	.01	.05	-						
8. EM Sad	.03	-.07	.00	.02	.34**	-.30*	.61**	-					
9. EM Happy	.22	.23	.29[4]	.08	.08	.01	.66**	.59**	-				
10. CAPS B	.61**	.40**	.89**	.88**	.06	.29*	.28[5]	-.12	.29*	-			
11. CAPS C	.55**	.39**	.79**	.67**	.06	.26	.18	.01	.21*	.65**	-		
12. CAPS D	.68**	.37**	.93**	.80**	.01	.36*	.29*	.01	.28	.75**	.75**		
13. CAPS E	.54**	.24	.87**	.71**	.00	.31*	.21*	.00	.18	.71**	.56**	.72**	
14. Age	-.37**	-.07	-.19	-.22	-.47**	.19	-.11	-.12	-.22	-.07	-.20	-.19	-.20

Note. Total PTSD severity as assessed by the CAPS-V and IES-R, total anxiety as assessed by the STAI and medication score is as described in section 2.1.8. EM = Emotional Modulation. No corrections for multiple comparisons are made, only planned correlation comparisons are interpreted. * = $p \leq 0.05$, ** = $p \leq 0.01$.

[4] $p = .056$
[5] $p = .056$

Table 12. *Regression Statistics Examining Relationships Between PTSD Symptom Scales and Pupil Responses in the Trauma Sample (n = 48)*

	B: Re-experiencing			C: Avoidance			D: Cognition and Mood			E: Arousal and Reactivity			
Criterion Variable	β	*t*	Unique sr^2	β	*t*	Unique sr^2	β	*t*	Unique sr^2	β	*t*	Unique sr^2	R^2 *p*
IPD	.11	0.42	.00	.10	0.44	.00	-.10	-0.65	.00	-.01	-0.25	.00	.01 .97
ICR													
Neutral	.02	0.06	.00	-.02	-0.07	.00	.29	1.06	.02	.10	0.44	.00	.05 .18
Emotional Modulation													
Fear	.18	0.74	.01	-.13	-0.58	.01	.29	1.01	.02	-.05	-0.23	.00	.01 .32
Sad	.05	0.20	.00	-.00	-0.00	.00	.05	0.19	.00	-.00	-0.02	.00	.00 1
Happy	.25	1.04	.02	-.03	-0.14	.00	.19	0.70	.01	-.11	-0.51	.00	.02 .91

Note. PTSD symptom severity assessed by the CAPS-V. β = standardised Beta. Unique sr^2 = the semi partial correlation (squared) representing unique variance. * = $p \leq 0.05$, ** = $p \leq 0.01$.

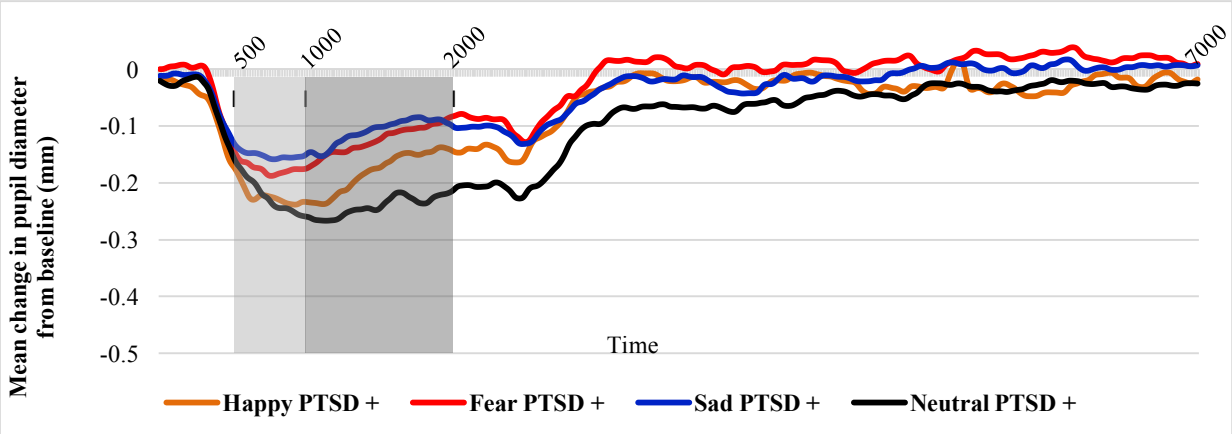

Figure 4. Mean change in pupil diameter from stimulus onset to 7000 ms for $n = 20$ participants in the PTSD positive group.

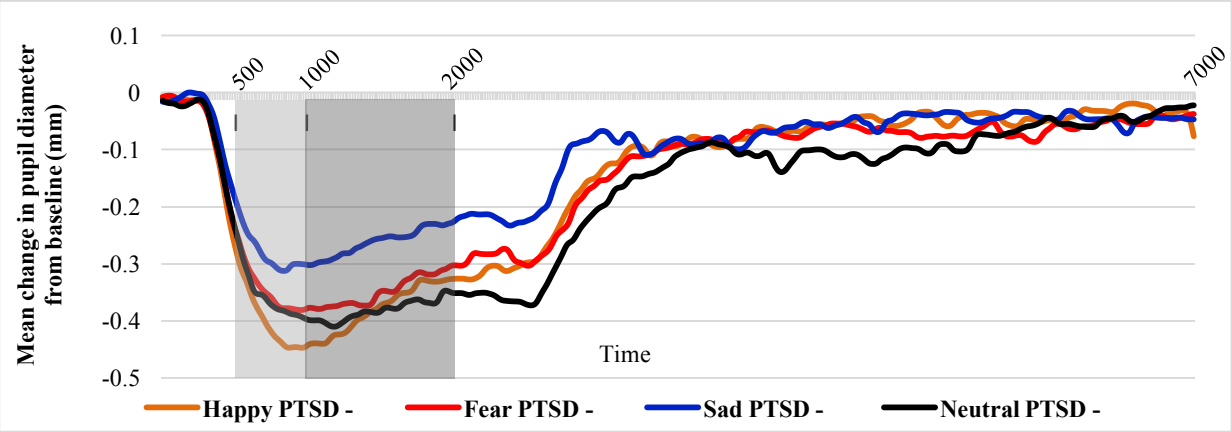

Figure 5. Mean change in pupil diameter from stimulus onset to 7000 ms for $n = 28$ participants in the PTSD negative group.

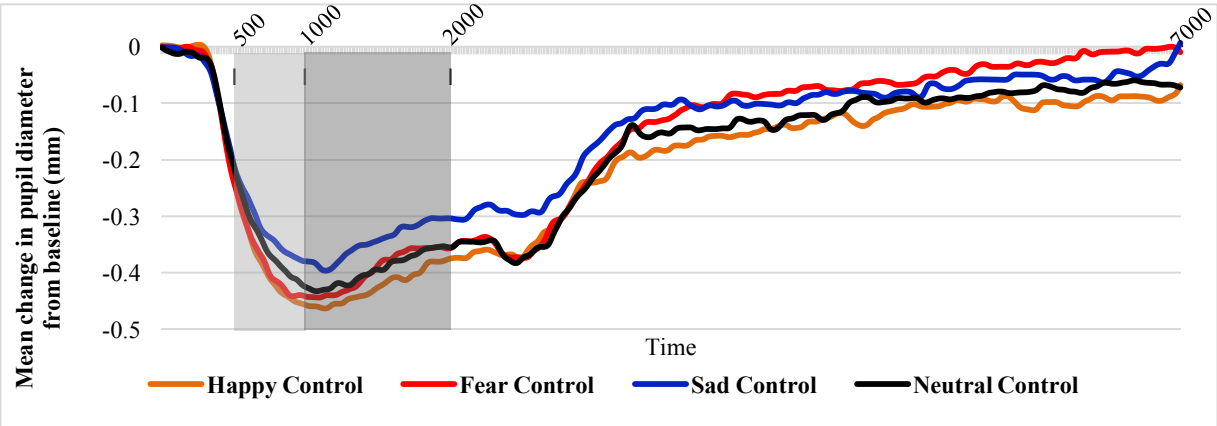

Figure 6. Mean change in pupil diameter from stimulus onset to 7000 ms for $n = 17$ participants in the control group.

3.2.5 Initial Constriction response 500 – 1000 ms

3.2.5.1 Missing data

Total missing data within this window, after data cleaning, was 8.79%.

3.2.5.2 Reliability

Correlational reliability analysis (corrected by Spearman-Brown; $2r$ / $1+r$) suggested good reliability for neutral (r = .92); happy (r = .93); sad, (r = .87); and fear, (r = .92) within this window.

3.2.5.3 Categorical Group Differences in the Initial Constriction Response to Neutral Images

A one-way ANCOVA to determine the effect of PTSD status on the ICR to neutral images was conducted, controlling for age. After adjustment for a significant effect of age (p =.014, there was a statistically significant effect of PTSD status on the ICR $F(2, 61) = 5.00$, p = .010, η_2 = .14. Planned comparisons, using corrected means, between PTSD positive (M = -0.19, SD = 0.22) and PTSD negative (M = -0.35, SD = 0.20) groups showed significant reduction in the ICR for PTSD positive participants (p = .006, d = 0.76). The planned comparison between the PTSD positive and Control group (M = -0.38, SD = 0.20) was also significant (p = .008, d = 0.91), demonstrating that only the individuals that had experienced a traumatic event and met criteria for PTSD showed this reduction in the ICR, with a large effect size. Graphs comparing ICR by group are displayed in Figure 7 and Figure 8.

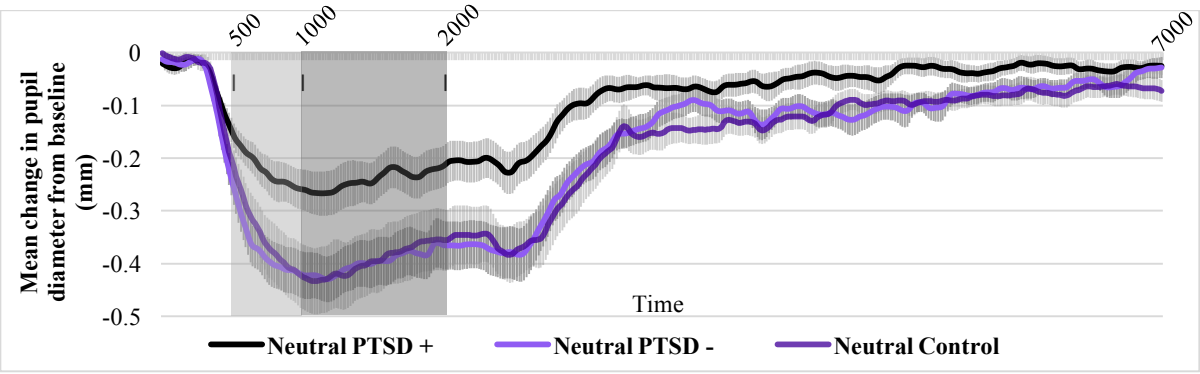

Figure 7. Comparison of pupillary response to neutral images across groups. The shaded area around the pupil response lines represent +/- 1 SEM.

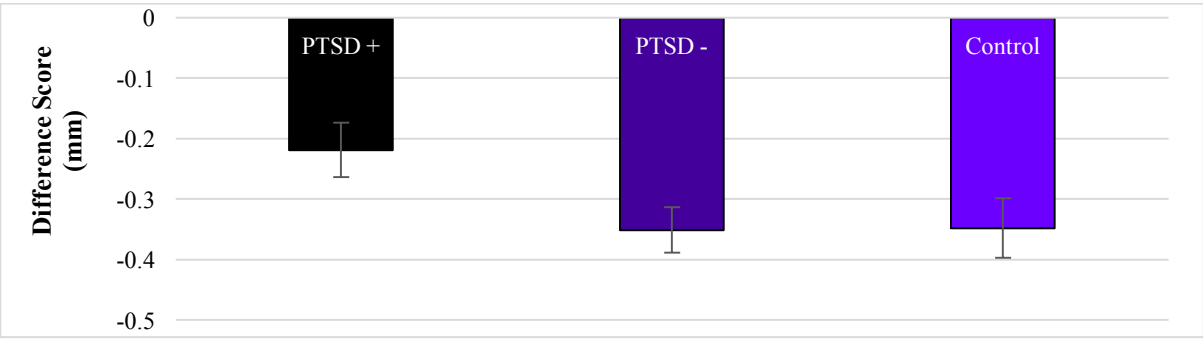

Figure 8. Mean ICR to neutral images by group within the 500 – 1000 ms window. Error bars represent +/- 1 SEM.

3.2.5.4 Dimensional Analysis of Initial Constriction Response

Analysis of zero-order correlations (Table 11) indicates that the ICR to neutral images was significantly associated with PTSD symptom severity from both the CAPS-V and self-report IES-R. The correlations suggest that the CAPS scales B, D and E were significantly related to the ICR. The ICR was also significantly related to anxiety.

To assess whether variation in ICR was uniquely related to any of the PTSD subscales, a multiple regression was conducted using the results from the neutral image category. PTSD symptom severity scales using the CAPS-V were the test variables, and ICR the criterion (see Table 12). Regression analysis indicated that none of the symptom severity scores were uniquely related to the ICR.

3.2.6 The Emotional Modulation Response 1000 – 2000 ms

3.2.6.1 Missing Data

Total missing data within this window, after data cleaning, was 10.15%.

3.2.6.2 Reliability

Correlational reliability analysis (corrected by Spearman-Brown; $2r$ / $1+r$) suggested good reliability for neutral (r = .88); happy (r = .89); sad, (r = .83); and fear, (r = .91) within this window.

3.2.6.3 Differential Emotional Modulation by Image Category

The effect of image type (happy, fear, sad and neutral) on pupil response within the 1000 – 2000 ms re-dilation period post stimulus onset was assessed within the whole sample. There was a significant main effect of image type, $F(2.62, 167.70 = 39.18$, $p <.001$, $\eta 2 = .38$. In comparison to the neutral images (M = -0.35, SD = 0.23), planned comparisons indicate greater pupil size to sad images (M = -0.23, SD = 0.23; $p < .001$, d = 0.52), fear images (M = -0.29, SD = 0.24; $p < .001$, d = 0.24) and a marginally significant difference to happy images (M = -0.33, SD = 0.25; p = .083, d = 0.08).

3.2.6.4 Categorical Group Differences in the Emotional Modulation of the Pupil

The emotional modulation score used in this section quantified the difference between emotional and neutral categories during re-dilation, and was necessary to avoid confounding by individual differences in constriction. A positive modulation score means that the pupil was more dilated while viewing an emotional image as compared to neutral.

A multivariate analysis of covariance (MANCOVA) to determine the effect of PTSD status (PTSD positive, PTSD negative and control) on the effect of emotional modulation (fear, happy and sad emotional modulation) was conducted, controlling for age. The effect of age was non-significant, so means are reported unadjusted. There was a significant main effect of pupil modulation by emotion F (6, 118) = 2.46, p = .028; Wilk's Λ = 0.790, partial $\eta 2$ = .11. Follow up univariate analyses with planned comparisons are reported below.

3.2.6.4.1 Fear images

A follow-up univariate test suggested a significant effect of PTSD status on the emotionally modulated pupil response by fear images $F(2, 61) = 4.62$, p =.014[6], $\eta 2$ = .13, see Figure 9 for a graphical representation of this result. Planned comparisons using unadjusted means showed that the PTSD positive group (M = 0.12, SD = 0.10) had greater emotional modulation than both the PTSD negative participants (M = 0.03, SD = 0.10; p = .006[7], d = 0.90), and the control group (M = 0.03, SD = 0.10; p = .019, d = 0.90).

3.2.6.4.2 Happy Images

A follow-up univariate test suggested a significant effect of group on the emotionally modulated pupil response for happy images $F(2, 61) = 3.32$, p =.043[8], $\eta 2$ = .10. (See Figure 12). Planned comparisons showed the difference between PTSD positive (M= 0.06, SD = 0.07) and PTSD negative groups (M= 0.001, SD = 0.09) was significant (p = .022[9], d = 0.73),

[6] Significant if adopting Bonferroni correction for 3 emotion comparisons (p < .017)
[7] Significant if adopting Bonferroni correction for 2 group comparisons (p < .025)
[8] Non-significant if adopting Bonferroni correction for 3 emotion comparisons (p < .017)
[9] Significant with Bonferroni correction for 2 group comparisons (p <.025)

as was the difference between PTSD positive and the control group (M= -0.06, SD = 0.06; p = .034[10], d = 1.85) (see Figure 10).

3.2.6.4.3 Sad Images

A follow-up univariate test suggested that there was no significant effect of group on the emotionally modulated pupil response for sad images $F(2, 61) = .24$, $p = .784$. This result is shown in Figure 11.

[10] Non-significant with application of Bonferroni correction for 2 comparisons ($p > .025$)

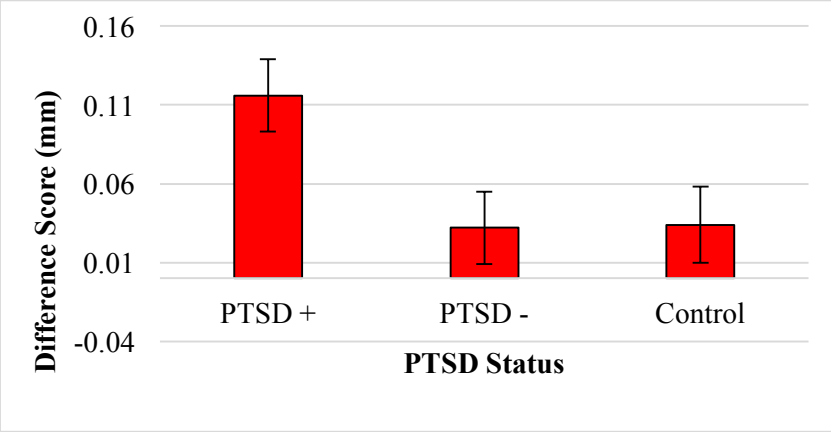

Figure 9. Group differences in the emotionally modulated pupil response to fear images. Error bars represent +/- 1 SEM.

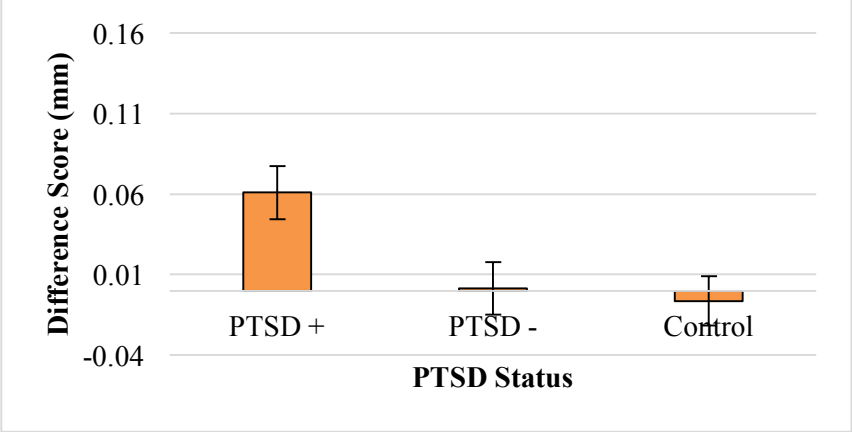

Figure 10. Group differences in the emotionally modulated pupil response to happy images. Error bars represent +/- 1 SEM.

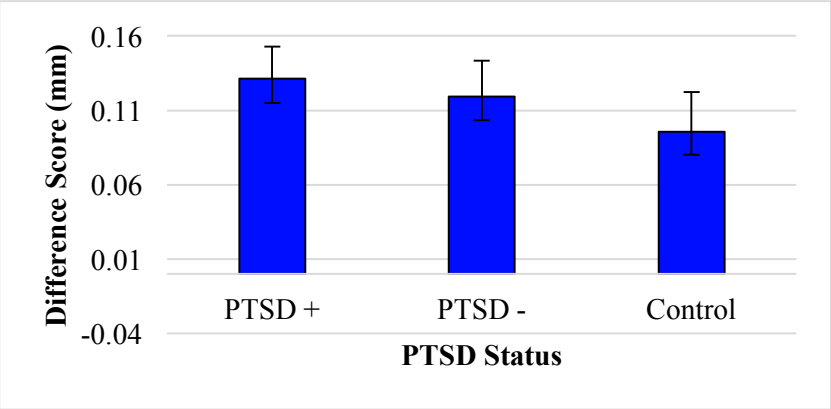

Figure 11. Group differences in the emotionally modulated pupil response to sad images. Error bars represent +/- 1 SEM.

3.2.6.5 Dimensional Analysis of Emotional Modulation

Analysis of zero-order correlations (Table 11) suggests a dimensional relationship between PTSD symptom severity and emotionally modulated pupil response for fear images using the CAPS-V, but not the IES-R. The CAPS B, D and E subscales were positively related to the emotionally modulated fear response also, suggesting that higher scores on these scales were related to more responsivity. The relationship to happy images paralleled the categorical results in producing a marginally significant result (p = .056), that was related to CAPS scales B and C.

To assess whether variation in any of the PTSD subscales were uniquely related to differences in emotionally modulated pupil dilation, multiple regressions were conducted. PTSD symptom severity scales using the CAPS-V were the test variables, and emotionally modulated pupil responses were the criterion variables. Inter-correlations are reported in Table 11 and regression statistics in Table 12. Despite the significant correlations, there were no significant relationships for subscale analyses, suggesting no unique relationship between the emotionally modulated pupil responses and specific scales.

3.2.7 Receiver Operator Characteristics Curves for the Prediction of PTSD

A signal detection paradigm was used to calculate the area under the curve (AUC) for the Receiver Operating Characteristic (ROC) – see Figure 12. The data was examined in the population of trauma exposed individuals (N = 48) for 1) emotional modulation to fear, 2) emotional modulation to happy and, 3) emotional modulation to sad images in the 1000 – 2000 ms

analysis period in which significant differences were found between those with and without PTSD. The ICR to neutral images was also assessed.

Prediction of PTSD using the emotionally modulated response to fear showed good predictive utility (AUC = .74, 95% CI .62 - .87, p = .002) which corresponds to a 'large' effect size (Rice & Harris, 2005). The emotionally modulated response to happy images was also predictive of group, with a similar effect size (AUC = .75, 95% CI .63 - .87, p = .001). The predictive utility of sad images was inadequate (AUC = .53, 95% CI .38 - .67, p = .744). The AUC value for the reduction in the ICR produced significantly above chance classification (AUC = .68, 95% CI .56 - .81, p = .022), though with a moderate effect size (Rice & Harris, 2005).

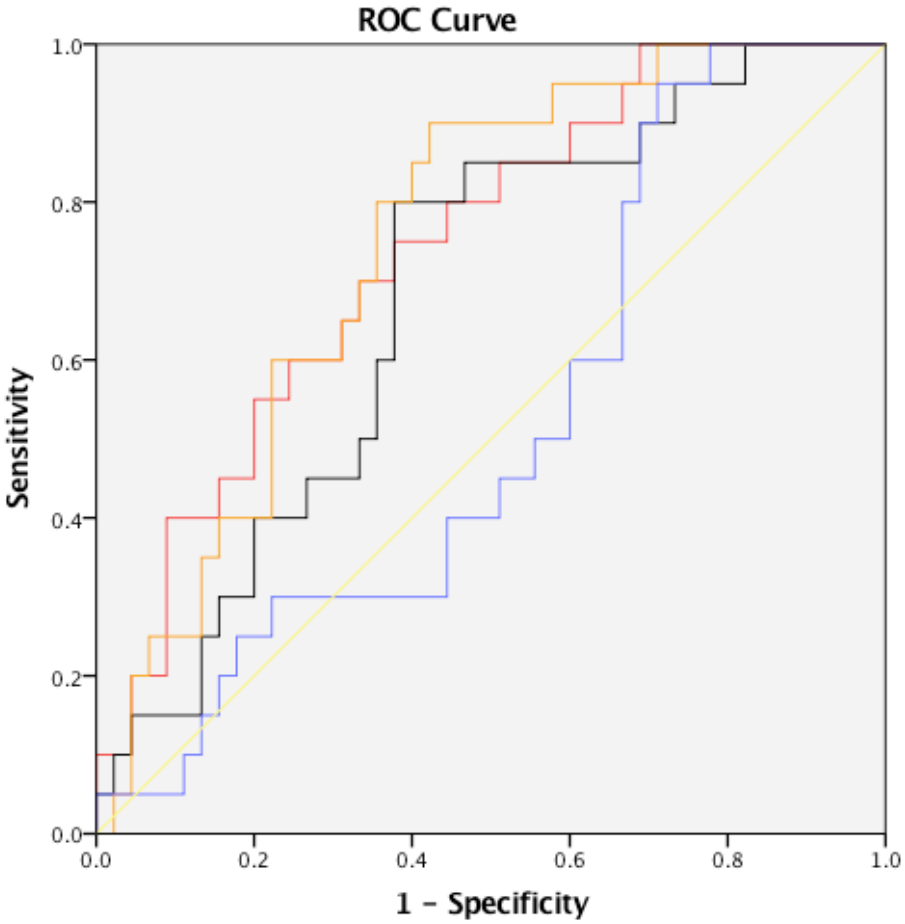

Figure 12. The Receiver Operator Characteristic (ROC) for the prediction of PTSD diagnostic status. Sensitivity (probability of PTSD for a high emotional modulation score) is plotted against 1-specficity (probability of no PTSD given a high emotional modulation score). The red line represents emotional modulated fear response, the orange line is the emotionally modulated happy response, the blue line is the emotionally modulated sad response, and the black line is the ICR to neutral images and

3.2.8 Discussion of Results

The results replicated a previous application of this study (O'Farrell, 2016) in showing that emotive images produce distinct patterns of emotionally modulated pupil constriction and re-dilation. The hypotheses that individuals with PTSD, in comparison to controls, would (1) show no abnormality in initial pupil diameter, (2) have a reduced initial constriction response, and (3) show more threat-specific pupil dilation was assessed with a passive image viewing task in three groups of individuals with and without PTSD. The analyses supported hypothesis one, two and three. The findings which are specific to Experiment One (hypotheses 2 - 3) are discussed in the following discussion paragraphs, and findings from hypothesis 1 are discussed in the general discussion following the addition of results from Experiment Two.

3.2.8.1 The Initial Constriction Response

The analysis of the ICR suggested that the PTSD positive group demonstrated significant reductions in amplitude, with a large effect size. The utility of the ICR to predict PTSD cases indicated that 68% of PTSD cases had a lower ICR than those without PTSD, which is considered a moderate effect size. The lack of group differences in the IPD is a strength, as individuals' ICR could not be said to be limited by a small resting pupil size (a 'floor effect'). The reduction in the constriction to neutral images was also related to higher symptom severity in dimensional analyses, but no specific subscale predicted this.

Comparable to the study by Bakes et al. (1990) the ICR was related to anxiety score. However, within this study the results suggest that the effect size for the relationship between PTSD symptoms and the ICR was larger than the relationship between reduced amplitude

and anxiety. The study of Bakes et al. differed in assessing pupil activity in the dark in a 'true' pupillary light reflex (PLR) paradigm. This kind of paradigm is more powerful in assessing a reduction in PLR amplitude, as the resting pupil is larger in darkness, and in presenting no stimulus which requires the lens to focus, such as the pictures used herein. Assessment in the dark was also not used in the current paradigm due to conditions of moderate light providing a more appropriate paradigm for the assessment of pupil dilation (Steinhauer et al., 2004), i.e. if the pupil is already maximally dilated as in conditions of darkness, this adds in a ceiling effect for the emotional modulation parameter. However, if a future study aimed to isolate the ICR then a dark paradigm would be appropriate, and it would be useful to replicate this finding, as it is the first study assessing the reduced constriction in PTSD.

Although there are no current published studies assessing the relationship between PTSD symptom severity and the ICR, a patent (US 20150289813 A1, 2015) titled *System and Method for the Biological Diagnosis of Post-Traumatic Stress Disorder: PTSD Electronic Device Application* has been approved by the US Patent Office. This device appears to focus on the threat-modulated reactivity of the pupil, but also suggests measurement of the light reflex. The patent also suggests that the device will be able to determine the likelihood that an individual suffers from PTSD. To create a diagnostic assessment with norms, the tool would require both validation and assessment of reliability, but there is no existing published work from this device, as of yet.

3.2.8.2 Emotionally Modulated Responses

A relationship between symptom severity and emotionally modulated dilation to fear images was supported in both the categorical and the dimensional analysis. Hence, the participants with PTSD showed greater pupil dilation to fear inducing stimuli.

The results appear in line with the finding of Cascardi et al. (2015), but the two paradigms differ in several important ways. First, the stimuli in Cascardi et al. were presented for a long time (30 s) and the dilation response was not isolated by a standardised analysis window, but was measured during fixations on specific threat elements of three images. Clearly, such a paradigm is prone to possible differences in fixation patterns. However, the long presentation time may have allowed for differences in the ICR (data not reported by Cascardi et al.) to have dissipated. Calculations of emotional difference scores were necessary herein to eliminate the confounding effect of the ICR. Snowden et al. (2016) demonstrated that increased pupil dilation for emotionally arousing images is independent of presentation time with display durations of 100 ms – 3000 ms, but no methodological papers have looked at longer display durations, and the reliability within these windows has never been assessed.

Second, the study of Cascardi et al. differed in that most of the sample were women who had been subject to violent traumas. Fifity-five percent of the current sample were men, and experiences of trauma varied widely due to the sampling technique. The differences between the studies, yet the common finding of a categorical difference add to the robustness of the finding, and the potential for the use of pupillometry in PTSD.

The emotionally modulated response to happy images also suggested greater emotional modulation in individuals with PTSD. This seems to suggest greater general reactivity in the individuals with PTSD. The ROC analysis represents the probability that a performance score (indices of pupil function) drawn from the PTSD population was higher than that of a non-PTSD population (Rice & Harris, 2005). Here, this discrimination probability suggested that individuals with PTSD had greater emotional modulation scores to happy and fear images and the effect size for this discrimination was large.

3.2.8.3 Implications

The reduction of the ICR in PTSD and in those scoring high on the dimensional measures (CAPS-V and IES-R) is suggestive of a reduction in parasympathetic arousal. Parasympathetic dysfunction is common to several psychiatric disorders and diseases. Wang et al. (2016) provide a review of studies and found 30 out of 36 report findings of PNS dysfunction or decreased PNS tone in a patient group versus healthy controls based on PLR measurements. The studies use various parameters (e.g., constriction amplitude and velocity) to index individual differences in parasympathetic function including Parkinson's disease (Fotiou et al., 2009; Granholm et al., 2003; Micieli et al., 1991), Alzheimer's disease (Fotiou et al., 2007; Fotiou, Fountoulakis, Tsolaki, Goulas, & Palikaras, 2000; Prettyman, Bitsios, & Szabadi, 1997), diabetes (Lanting et al., 1990; Smith & Smith, 1983; Smith, Smith, Brown, Fox, & Sönksen, 1978) and schizophrenia (Bär et al., 2008). Reduction in the PLR amplitude has also been demonstrated in anxiety (Bakes et al., 1990) and autism (Daluwatte et al., 2013).

3.2.8.4 Limitations

The demographics of the samples were well matched on most variables, but not perfectly matched on age due to quasi-experimental, opportunistic sampling. This confound, and the relationships to outcome variables, was carefully considered and statistically controlled for within all analyses. The use of two comparison groups was also useful in overcoming these limitations, as the patterns of significant results can be compared to both PTSD negative and control groups with slightly different demographics.

This study was also not a 'true' ophthalmologic assessment of the PLR for reasons discussed above, although emotional (sympathetic) influences on constriction were removed by using the neutral stimuli. Future research would benefit from assessment after dark adaption and from using a stimulus which does not require the lens to focus.

3.3 Experiment Two: Pupillometry to Affective Sound Clips

The studies outlined in section 3.1.2.4 use visual stimuli to assess threat reactivity in post-traumatic stress disorder. Studies assessing pupil dilation during cognitive processing using non-visual stimuli (e.g., while doing calculations; Granholm & Steinhauer, 2004), show that cognitive pupillometry is not limited to visual stimulus paradigms. Pupil activity to non-visual stimuli has the advantage of removing optical influences on the pupil which produce the light reflex. However, research assessing pupil dilation to affective sounds is limited.

Dabbs (1997) investigated the potential moderating effect of testosterone on arousal (measured via pupillary dilation) to erotic sounds. The stimuli were limited, consisting of four 30 second sound clips; two neutral, one aggressive, and one sexual. The authors found greater pupil dilation to the sexual sound clip, and concluded that auditory stimuli were valid for pupillometry studies.

The International Affective Digitised Sounds (IADS; Bradley & Lang, 2000) has since been developed and validated to assess physiological arousal to naturally occurring noises, such as screams, laughter, music and machinery. Partala, Jokiniemi and Surakka (2000) investigated pupil size during processing of groups of sounds. The authors combined 10 sounds to form categories of highly positively and negatively arousing versus neutral sound clips. In comparison to the neutral clips, the pupil was significantly larger during the positive and negative sounds. They conclude that the autonomic nervous system is sensitive to the affective content of sounds, and that pupil size variation is an appropriate outcome measure.

More recent studies have assessed music induced arousal, for example individual differences in musical preference and emotional "chill" responses to music using pupillometry (Gingras, Marin, Puig-Waldmüller, & Fitch, 2015; Laeng, Eidet, Sulutvedt, & Panksepp, 2016).

Burley (2016) developed and employed a pupillometry to affective sounds task to assess the relationship between emotional arousal and psychopathic traits (reported in a PhD thesis and published within Burley et al. 2017). The task built on those of Dabbs (1997) and Partala et al. (2000) by controlling the decibel level of the sound clips and in using the measure to assess individual differences in emotional responsivity. The task development demonstrated emotional modulation; demonstrating that negative sounds produced distinct patterns of pupil dilation, and significantly more dilation than neutral and positive sounds.

The study outlined below aimed to assess differences in pupillary response according to PTSD diagnostic status, and assess the relationship between PTSD symptom severity and indices of pupillary function using a passive listening sound clip paradigm. Sound clips with unpleasant, pleasant and neutral content were played whilst pupil diameter was recorded to assess whether arousal associated with PTSD symptoms is threat-specific, if there is a blunted response to positive imagery, and to provide measures of resting pupil diameter. The use of pupillometry to sound clips has not been reported in a trauma population prior to this study.

3.3.1 Hypotheses

Within the task assessing pupil responses to emotive sound clips it is hypothesised that individuals with PTSD;

1. Will not differ from controls in their level of initial pupil dilation. There will be no relationship between initial pupil diameter and symptom severity.
2. Will show greater arousal to unpleasant sounds during pupil re-dilation. Higher levels of PTSD symptom severity would be related to greater emotional modulation of the pupil by unpleasant sounds. This will be indexed by the difference between the pupil size to the unpleasant stimuli and the neutral stimuli.

Exploratory analyses will be performed for the pleasant sounds comparison stimuli.

3.3.2 Method

3.3.2.1 Sample and exclusions

Details of the full sample can be found in Chapter 2. During data analysis, nine individuals were excluded due to >50% missing data within any analysis window, one individual was excluded due to extreme outlier values across two or more variables, and one individual was excluded due to multivariate outliers within pupillary data (Mahalanobis distance = 25, *df* = 3) yielding a final sample of sixty-two individuals[11] (*n* = 20 PTSD positive; 26 PTSD negative; 16 control). Full demographics are reported in Chapter 2 and a summary of key demographic variables is presented in Table 13 below, after exclusions.

[11] The pattern of results was consistent when including individuals removed due to violation of statistical assumptions.

Table 13. *Age, Gender and IQ Demographics for Experiment Two*

	PTSD Positive (*n* = 20)	PTSD Negative (*n* = 26)	Control (*n* = 16)	Internal consistency
Age	37.79 (*9.85)*	44.58 *(14.76)*	50.10 *(12.76)*	
Gender	50% female	42% female	44% female	
IQ	101.76 *(20.39)*	104.56 *(17.11)*	108.14 (*23.00)*	
CAPS-V	40.89 *(13.88)*	7.00 *(8.40)*	-	.95
IES-R	54.95 *(15.90)*	16.27 *(19.18)*	9.87 *(19.51)*	.97

Note. Mean *(Standard deviation)*. Internal consistency assessed by Cronbach's alpha

3.3.2.2 Materials

The psychometric and assessment measures used are reported in Chapter 2. The experimental paradigm employed was developed by Burley (2016), and full details of task piloting, development and use in both a community sample and a sample of forensic and psychiatric inpatients are reported within the thesis (section 3.5.1 for methods). Task results are also detailed in Burley et al. (2017). The task consisted of 30 sound clips selected from the IADS[12], divided into three valence categories and presented in a pseudo-random order. The categories were formed of unpleasant, pleasant and neutral sounds. Pleasant and neutral sound clips were matched on dimensions of arousal, and the unpleasant sounds were significantly more arousing. Affective sound-clips that were classified as unpleasant or pleasant were based on Stevenson and James' (2008) 'fearful' and 'happy' categories, and

[12] IADS sound-clips were: Unpleasant: 106, 115, 310, 424, 600, 625, 626, 712, 714, 732; Pleasant: 220, 311, 352, 353, 360, 365, 415, 808, 815, 817; Neutral: 120, 152, 170, 246, 361, 364, 368, 425, 500, 701.

neutral sound-clips based on mid-point valence ratings. Unpleasant sound clips included growling, bees, an angry crowd, car wreck, bike wreck, mayday, explosion, buzzers, sirens and crashing. Pleasant sounds included excited sports crowds, laughter, roller coasters and music. The neutral category included animal sounds, nature, background noise, heart beats, chattering crowds, transport, wind and fan noise.

As reported in Burley et al., sounds were matched on the root mean square decibel and peak decibel levels to remove any potential artefact of altered pupil size and noise level. Each 6000 ms sound clip was played while participants were presented with a blank grey screen containing an isoluminant fixation cross (see Figure 11). Prior to the stimulus onset a blank grey screen was presented for 2000 ms. This blank screen included a fixation mark for the first 1000 ms. The same blank screen was presented for 8000 ms following the stimulus to allow the pupil to return to baseline.

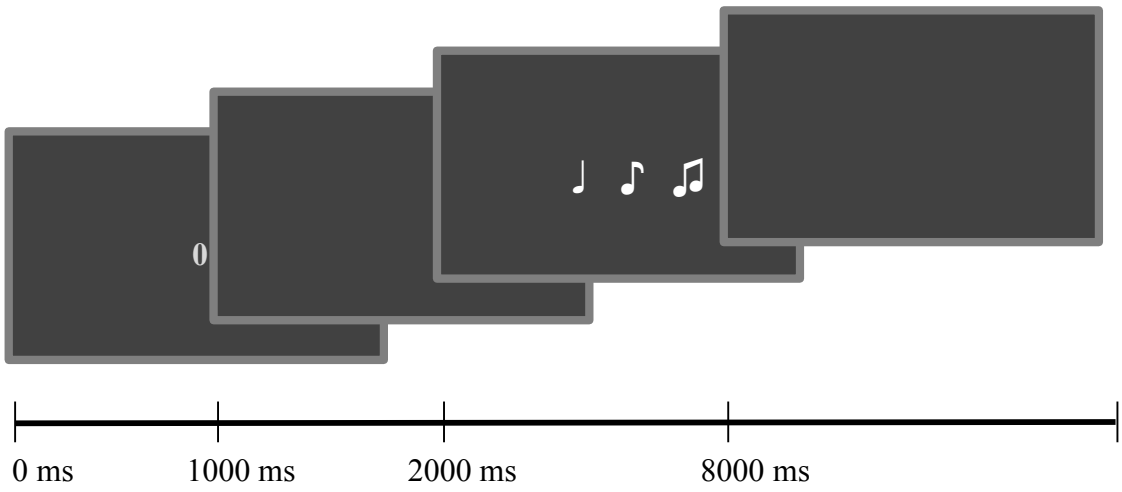

Figure 13. Visual representation of an experimental trial. Musical notes indicate the time period in which the sound clip was played.

3.3.2.3 Procedure

The general study procedure can be found in Chapter 2 and general eye tracking procedure in section 3.2.2.3, presentation hardware and software in section 3.2.2.4, and data cleaning methods in section 3.2.2.5. Participants were informed that although there would not be anything on the screen, they should focus on the fixation cross and should not take their eyes away from the screen at any point. Participants were informed that the task would take just over eight minutes, asked to pay attention throughout, and advised that they could blink during the task.

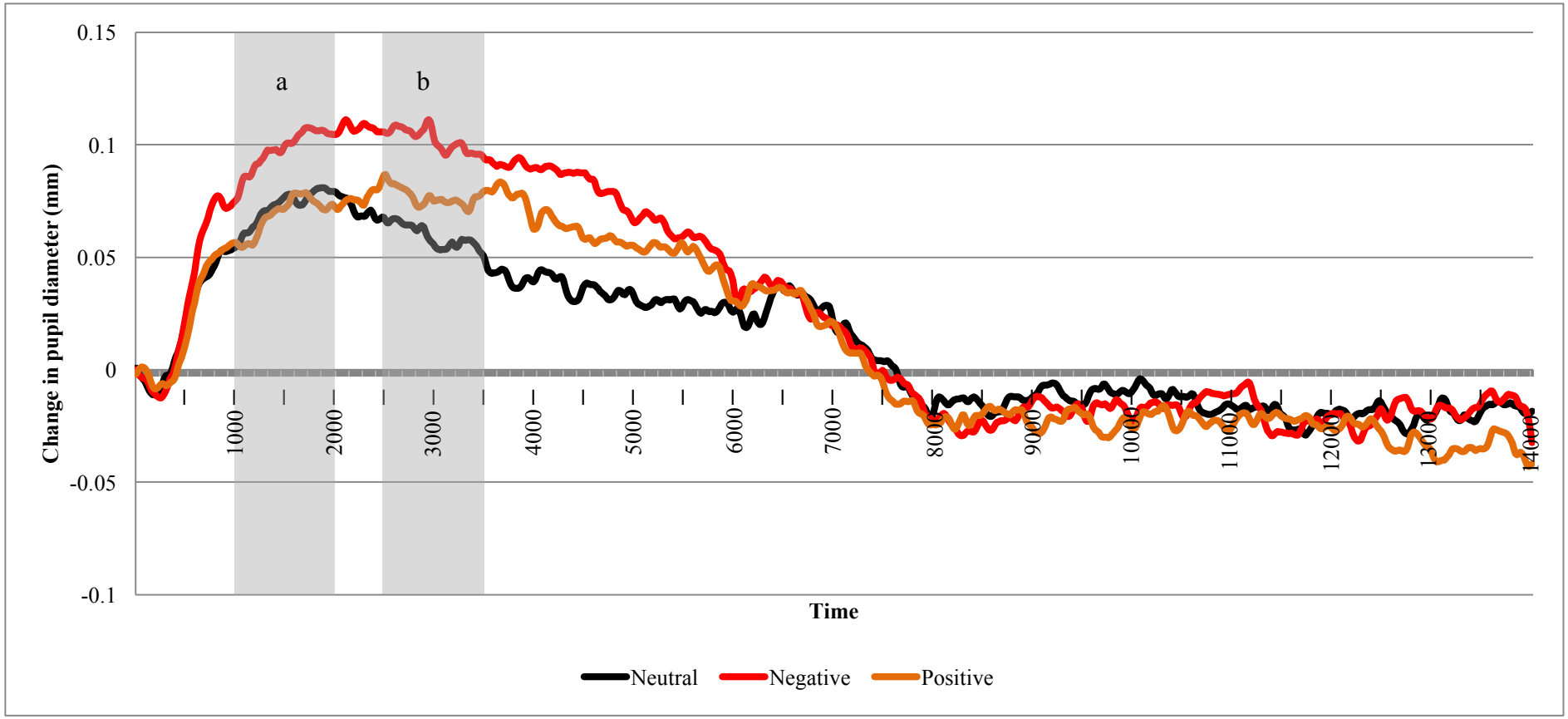

Figure 14. Mean change in pupil diameter from stimulus onset to 14,000 ms for $N = 62$ participants. Stimulus offset occurred at 6000 ms. The shaded areas represent the two analysis windows of interest. a = 1000 – 2000 ms; the early period b = 2500 – 3500 ms; the late period.

3.3.3 Results

3.3.3.1 Order of Analyses

Analysis of initial pupil dilation (IPD; 200 ms prior to stimulus onset) is conducted first, followed by the early dilation period (1000 – 2000 ms post stimulus onset), followed by the late dilation period (2500 – 3500 ms post stimulus onset). The early analysis period is retained from Experiment One and the late analysis window was used by Burley (2016) as a period of clear differentiation in pupil modulation by emotive category across sound clip types. A graphical representation of analysis windows is shown in Figure 14.

3.3.3.2 Statistical Analyses

The covariates are reported in section 3.2.3.2 and methods of statistical analysis are reported in section 3.2.3.3.

3.3.4 Initial Pupil Diameter

3.3.4.1 Missing data

Total missing data within this window, after data cleaning, was 13.22%.

3.3.4.2 Reliability

Correlational reliability analysis (corrected by Spearman-Brown; $2r$ / $1+r$) suggested almost perfect reliability for initial pupil response (r = .99). The relationship between IPD measures taken from both experimental paradigms (images and sounds) suggested excellent

test re-test reliability (r =.91, p = .001). The test-retest interval varied from thirty minutes to one hour.

3.3.4.3 Categorical Analysis of Initial Pupil Diameter

An ANCOVA was used to determine the effect of PTSD status on IPD, controlling for age. After adjustment for age (p = .011), there was no significant difference in IPD across groups, suggesting no differences in the IPD were attributable to PTSD status between the PTSD positive (M = 3.33, SD = 0.60), PTSD negative (M = 3.57, SD = 0.68) and control (M = 3.51, SD = 0.68) groups $F(2, 58) = 0.78$, p = .463.

3.3.4.4 Dimensional Analysis of Initial Pupil Dilation

Analysis of zero-order correlations (Table 14) indicates that IPD was not significantly associated with any outcome variables, but was negatively associated with age. Age has been included as a covariate, as was the case in Experiment one.

To assess whether any of the PTSD subscales were uniquely related to the IPD, a multiple regression was conducted. PTSD symptom severity scales using the CAPS-V were the test variables, and IPD the criterion (see Table 15). Regression analysis indicated that none of the symptom severity scores were uniquely predictive.

Table 14. *Zero-order Correlations Between PTSD Severity, Total Anxiety, Medication and Pupil Responses within the sample (N = 62 for measures not using the CAPS, n = 46 for CAPS measures)*

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1. Total Anxiety	-												
2. Medication score	.53**	-											
3. PTSD Severity CAPS-V	.74**	.47**	-										
4. PTSD Severity IES-R	.71**	.39**	.88**	-									
5. IPD	-.04	.06	.04	.18	-								
6. EM Early Unpleasant	.10	-.04	-.04	.03	.17	-							
7. EM Early Pleasant	.25*	.02	.16	.23	-.07	.47**	-						
8. EM Late Unpleasant	.16	.09	.06	.00	.06	.67**	.29*	-					
9. EM Late Pleasant	.19	.00	.18	.20	.04	.41**	.76**	.49**	-				
10. CAPS B	.66**	.48**	.90**	.88**	.05	-.04	.23	.01	.19	-			
11 CAPS C	.61**	.44**	.80**	.69**	.16	.07	.09	.13	.13	.67**	-		
12 CAPS D	.77**	.47**	.93**	.80**	-.01	-.04	.06	.10	.10	.76**	.77**	-	
13 CAPS E	.57**	.28	.88**	.71**	.01	-.08	.16	-.10	.23	.71**	.57**	.73**	-
14. Age	-.30*	.00	-20	-.22	-.29*	-.20	-.17	-.21	-.37**	-.05	-.24	-.24	-.20

Note. EM Early = Emotional modulation within the 1000 – 2000 ms window. EM Late = Emotional modulation within the 2000 – 3500 ms window.

* $p \leq 0.05$, ** $p \leq 0.01$

Table 15. *Regression Statistics Examining Relationships Between PTSD Symptom Scales and Pupil Responses to Sound Clips in the Trauma Sample (n = 46)*

	B: Re-experiencing			C: Avoidance			D: Cognition and Mood			E: Arousal and Reactivity			
Criterion Variable	β	*t*	Unique sr^2	β	*t*	Unique sr^2	β	*t*	Unique sr^2	β	*t*	Unique sr^2	R^2 *p*
IPD	.05	0.20	.00	.38	1.59	.06	-.34	-1.14	.02	.00	0.01	.00	.07 .59
Emotional Modulation Early													
Unpleasant	-.05	-0.18	.00	.27	1.10	.03	-.14	-0.47	.01	-.10	-0.41	.00	.04
Pleasant	.39	1.53	.05	.01	0.07	.00	-.32	-1.07	.03	.11	0.45	.00	.08 .44
Emotional Modulation Late													
Unpleasant	-.14	-0.65	.01	.16	0.65	.01	.19	0.64	.01	-.14	-0.59	.01	.04 .78
Pleasant	.14	0.55	.00	.09	0.38	.00	-.30	-1.00	.02	.30	1.27	.04	.08

Note. PTSD symptom severity assessed by the CAPS-V. β = standardised Beta. Unique sr^2 = the semi partial correlation (squared) representing unique variance. * $p \leq 0.05$, ** $p \leq 0.01$.

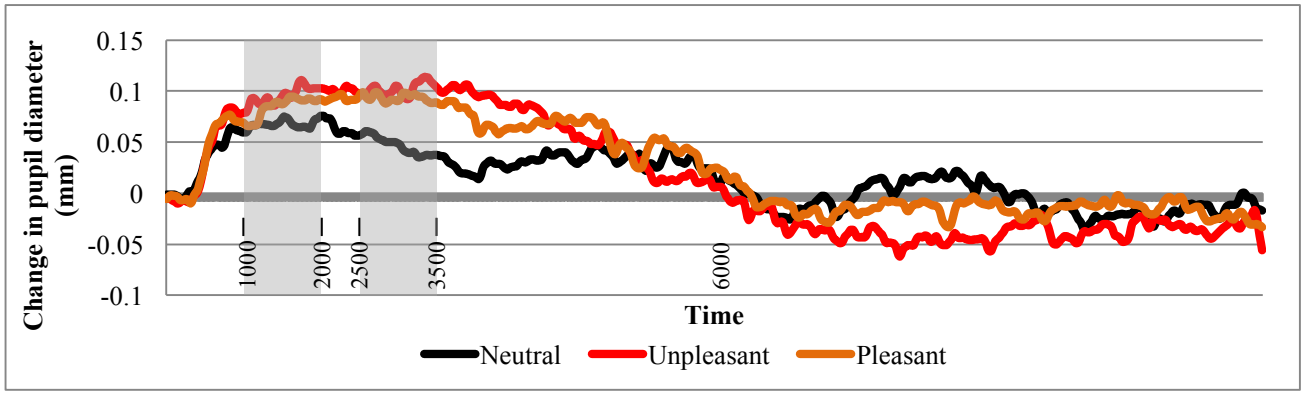

Figure 15. Mean change in pupil diameter from stimulus onset to 14,000 ms for $n = 20$ participants in the in the PTSD positive group.

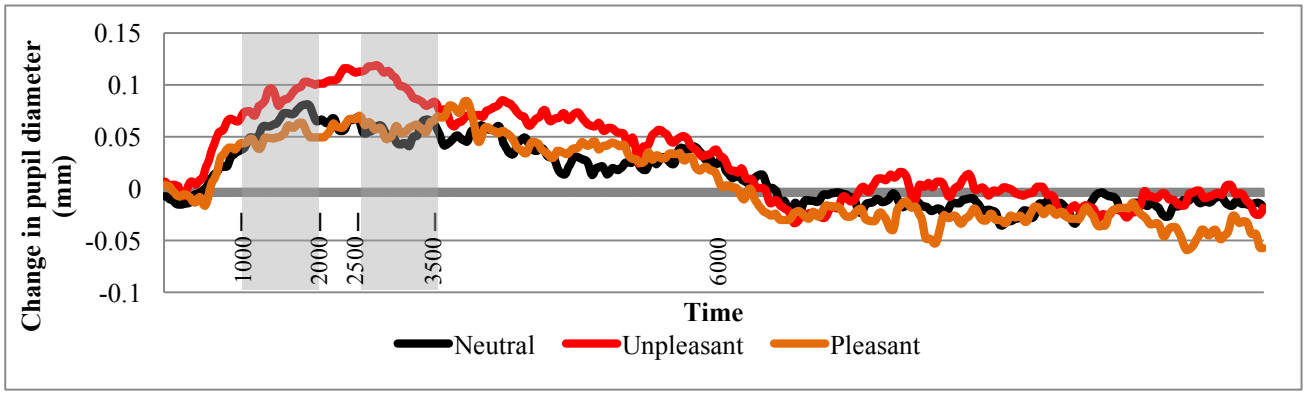

Figure 16. Mean change in pupil diameter from stimulus onset to 14,000 ms for $n = 26$ participants in the in the PTSD negative group.

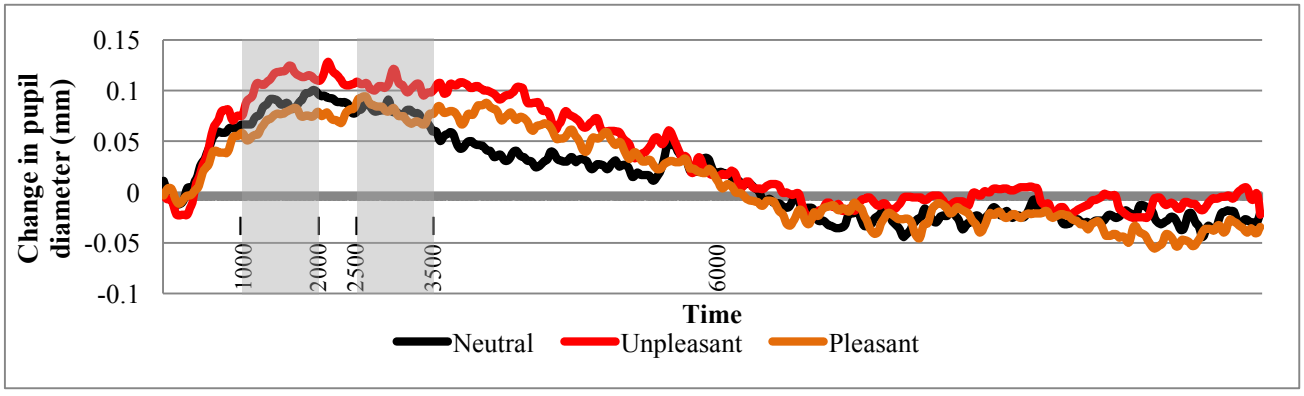

Figure 17. Mean change in pupil diameter from stimulus onset to 14,000 ms for $n = 16$ participants in the in the control group.

3.3.5 Early Emotional Modulation 1000 – 2000 ms

3.3.5.1 Missing data

Total missing data within this window, after data cleaning, was 11.02%.

3.3.5.2 Reliability

Correlational reliability analysis (corrected by Spearman-Brown; $2r$ / $1+r$) suggested acceptable reliability for unpleasant stimuli (r = .57) but poor reliability for neutral (r = .40) and pleasant (r = .19) pupillary responses within this window.

3.3.5.3 Emotional Modulation by Sound Category

There was a significant main effect of sound clip emotion, $F(2, 122) = 4.94$, $p = .009$, $\eta 2 = .08$ (see Figure 14). Planned comparisons showed that unpleasant sounds (M = 0.10, SD = 0.10) produced more dilation than neutral sounds (M = 0.07, SD = 0.07; p = .020, d = 0.38). There was no difference between neutral and pleasant sounds (M = 0.07, SD = .07; p = .693).

3.3.5.4 Categorical Group Differences in the Emotional Modulation of the Pupil

A one-way multivariate analysis of covariance (MANCOVA) to determine the effect of PTSD status on the emotional modulation to sound clips (unpleasant or pleasant less neutral) was conducted, controlling for age. The effect of age was non-significant (p = .277). There was no significant main effect of pupil modulation by group F (4, 114) = 0.65, p = .628; Wilk's Λ = 0.96, therefore further comparisons have not been conducted. Graphs displayed in Figure 15 - Figure 17 illustrate the pupil waveforms by PTSD diagnostic status group.

3.3.5.5 Dimensional Analysis of Early Emotional Modulation of the Pupil

Analysis of zero-order correlations (Table 14) indicate no dimensional relationships between PTSD symptom severity and emotionally modulated pupil response to sounds using the CAPS-V or IES-R. The CAPS subscales were not related to the emotionally modulated responses.

To assess whether variation PTSD subscale scores were uniquely related to variation in emotionally modulated pupil responses multiple regressions were conducted. PTSD symptom severity scales from the CAPS-V were the test variables, and emotionally modulated pupil responses were the criterion variables (see Table 15). As the non-significant correlations suggested, there were no significant relationships for subscale analyses, suggesting no unique relationship between the emotionally modulated pupil responses and specific scales.

3.3.6 Late Emotional Modulation 2500 – 3500 ms

3.3.6.1 Missing Data

Total missing data within this window, after data cleaning, was 12.90%.

3.3.6.2 Reliability

Correlational reliability analysis (corrected by Spearman-Brown; $2r$ / $1+r$) suggested unacceptable reliability for neutral (r = .20); pleasant (r = .00); and unpleasant, (r = .48); pupil responses within the re-dilation window.

3.3.6.3 Emotional Modulation by Sound Category

There was a significant main effect of sound clip type, $F(2, 122) = 6.08$, $p = .002$, $\eta 2 = .18$, suggesting differential pupil diameter between sound clips. Planned comparisons suggest that unpleasant sounds (M = 0.10, SD = 0.10) produced more dilation than neutral sounds (M = 0.06, SD = 0.08; p = .001, d = 0.46). There was no difference between neutral and pleasant sounds (M = 0.07, SD = .06; p = .264). Results paralleled the early window, but with larger effect sizes.

3.3.6.4 Categorical Group Differences in the Late Emotional Modulation of the Pupil

A one-way MANCOVA to determine the effect of PTSD status (PTSD positive, PTSD negative, and control) on the effect of emotional modulation to sound clips (unpleasant or pleasant less neutral) was conducted, controlling for age. Controlling for a significant effect of age (p = .031), there was no significant main effect of pupil modulation by group $F(4, 114) = 0.88$, p = .478; Wilk's Λ = 0.94. Therefore, further comparisons have not been conducted.

3.3.6.5 Dimensional Analysis of Late Emotional Modulation of the Pupil

Analysis of zero-order correlations (Table 14) indicate no dimensional relationships between PTSD symptom severity and emotionally modulated pupil response to sounds during the late period. The CAPS subscales were not related to the emotionally modulated responses.

There were no significant relationships for subscale analyses, suggesting no unique relationship between the emotionally modulated pupil responses and specific scales.

3.3.7 Discussion of Results for Experiment Two

The analysis replicated previous applications of this study (Burley, 2016; Burley et al. 2017) in showing that unpleasant emotive sounds produce distinct patterns of emotionally modulated pupil dilation. The hypotheses that individuals with PTSD would; (1) show abnormality in initial pupil diameter, and (2) show increased emotional modulation of the pupil while listening to unpleasant sound clips were assessed within a sample of trauma exposed individuals. The analyses supported hypothesis one, but there were no statistically significant effects supporting hypotheses 2.

3.3.7.1 Limitations

The levels of emotional modulation were lower in this task, as demonstrated by the magnitude of the effect sizes between for the pupil response to emotional versus neutral scores. The reliability of the pattern of pupil response produced by sound clips was generally poor within this task. This contrasts with the reliability reported in response to images in Experiment One, and to the acceptable reliability reported in the studies conducted by Burley (2016). The visual images task produces a robust light reflex response, which is highly reliable, and undoubtedly influenced the high levels of reliability reported in the images task. The missing data values were comparable to that of Burley (2016), suggesting poor data cannot have resulted in lower reliability. Limited reliability of physiological responding is suggested by Arena, Blanchard, Andrasik, Cotch, and Myers (1983) using varying test-retest intervals, and this lack of reliability is suggested to limit the extent to which physiological measures could be used as individual assessments (rather than to assess differences within a group or between groups). Lack of reliability could suggest inconsistent emotional responses between stimuli in the same category, meaning that sound clips within the same ‘category’ do

not elicit the same response. It is also possible that the sounds used in this paradigm did not 'interact' with PTSD symptoms. Given the lack of reliability in the data set, it is not surprising that the paradigm was unable to demonstrate significant differences between groups.

3.3.8 Overall Discussion of Cognitive Pupillometry to Affective Images (Experiment One) and Affective Sounds (Experiment Two) in PTSD

3.3.8.1 Cross Task Comparisons

3.3.8.1.1 Task Methodology

Evidence for enhanced emotional modulation to affective stimuli in individuals with PTSD was demonstrated in Experiment One using affective images, while there was no evidence to support this hypothesis using affective sound stimuli in Experiment Two. The lack of result in the auditory task is not suggested to represent a modality-specific sensitivity limited to emotive images, but is suggested to be due to differences in the experimental sounds paradigm, including reliability, as discussed in section 3.3.7.1. Within the emotive sounds task, the unpleasant category may not have represented direct threat as much as the images did due to ethical constraints reported by Burley (2017) during task development. The strength of the auditory stimuli was reduced during consultation with clinicians for ethical purposes (for example, no longer playing sound clips of screaming contained within the IADS). This lowered the stimulus strength and reduced effect sizes of the difference between emotional and neutral in the auditory task in comparison to the images task which, in

combination with poor reliability in these experiments, reduced the potential to detect an effect in the affective sounds task.

Another potential cross-task difference is the extent to which the stimuli 'interact' with PTSD symptoms. These studies did not employ ideographic trauma stimuli, in contrast to studies assessing physiology during script driven imagery (Hopper, Frewen, van der Kolk, & Lanius, 2007; Lanius et al., 2002) as the study design required a generic stimulus set due to opportunistic recruitment and ethics. It is possible that the image task stimuli represented direct threat (for example, dangerous animals and human violence), whereas the sounds task contained stimuli which were considered unpleasant, but not directly threating (for example, sirens, angry crowd, buzzing and crashing).

The results of Experiment One showed that individuals with PTSD were more reactive to both the fear and happy categories, suggesting general reactivity, rather than the threat specific sensitivity which had been predicted. However, this enhanced sensitivity was not apparent for the sad images, possibly due to a ceiling effect, as these were the most emotive images (consistent with O'Farrell, 2016). To test this prediction a more strongly arousing category could also be introduced, such as erotic images. However, this stimulus category would not be suggested to interact with PTSD symptoms and may present ethical concerns in cases where trauma occurred after sexual violence. It may be the case that threat-specific sensitivity would only be demonstrated if stimuli were ideographic and of a greater emotive value to interact with individual trauma memory, but no pupillometry and PTSD studies have explored this yet. Future research or adaptations for clinical assessment could consider trauma specific stimulus sets, such as motor vehicle accidents, war, or interpersonal

violence. Specific stimulus sets could then be used to measure reduction in PTSD symptoms over time within individuals.

3.3.8.1.2 Initial Pupil Dilation Across Tasks

The IPD was not significantly related to any outcome measures of interest, including assessed and self-reported PTSD severity and anxiety. Bakes et al. (1990) found no significant difference in resting pupil size after dark adaption in individuals with anxiety versus controls and Felmingham et al. (2011) found no differences between individuals with and without PTSD assessed in a lit room. Hence, there are no existing published studies reporting alterations in baseline pupil size in PTSD, despite much anecdotal reporting of larger pupils. A study by Bitsios et al. (1996) found increased resting pupil diameter during fear-conditioning, suggesting larger IPD can be linked to task-related fear, and that IPD is associated with state measures, rather than more stable traits or chronic symptoms. Interestingly, resting pupil diameter has been written in as an outcome measure within a pre-registered clinical trial ('A Pilot Dose-Response Biomarker Study of Brexpiprazole Treatment in PTSD', 2017). The rationale is not included, nor is the specific pupil methodology, but the study aims to recruit individuals with a CAPS-V severity score of over 40 and assess symptoms before and after a 6-week pharmacological treatment trial. The current study results, grouped in this way for Experiment One, suggest that there are no group differences in baseline pupil diameter in individuals with a CAPS-V score of 40 and over and trauma-exposed individuals with a range of lower CAPS-V scores (see supplementary analysis Appendix B, section 2.1.1). The current results suggest no effect of PTSD on IPD, but whether baseline pupil dilation can be sensitive to reductions in symptom severity in a within-subjects design remains to be seen. A clinical trial design should be powerful enough

to reveal effects on resting pupil diameter, should there be any, and add to the limited, but converging, experimental evidence within this area.

3.3.8.1.3 Emotional Modulation of the Pupil

Experiment one supported an effect of PTSD on emotional modulation by fear images and an emotional modulation of the pupil while viewing happy images, but no statistically significant difference for sad images. Both significant findings had a large effect size. The inclusion of the 'sad' category here was useful in determining whether the effect of negative stimuli was specific to threatening images, or was a general arousal effect. Results for the sad images produced the largest emotional modulation effect size (section 3.2.6) and the three groups showed comparable modulation. It is possible that the high levels of emotional modulation from the sad images produced a ceiling effect, obscuring any potential individual differences in reactivity.

The outcome measures and results from these experiments do not suggest that individuals with PTSD have 'larger pupils' than those without, but that they were more reactive to fear and happy image categories than neutral. Analysis of results using either the raw pupil size or baseline corrected pupil size would not be informative here due to the reduction in the constriction of the pupil which was found to be associated with PTSD. As an artefact of this finding, individuals with PTSD have consistently 'larger' pupils during these small analysis periods in the visual images task. The lack of this result in Experiment Two could suggest that neutral sounds were more stimulating than neutral pictures, reducing the power to detect a difference, or that emotive sounds are less stimulating that emotive pictures, or it could be an artefact of the experimental method, for example, the poor internal reliability of the emotive categories.

3.3.8.1.4 Reliability and Validity of Self-Report versus Structured Interviews

Appendix B, section 2.1.2 assessed the similarities and differences between results using self-reported symptoms, as assessed by administration of the IES-R as compared to results reported in Experiment One using the CAPS-V interview. Experiment one was chosen for this supplement due to the significant results discussed above. Analyses using self-reported PTSD symptoms support a reduction in the ICR and suggest that emotional modulation to fear images is larger in individuals grouped by an IES-R cut off score (> 37). These findings are consistent with results from the interview based PTSD scores, in that they demonstrate the same trends, but they fail to reach significance for all the happy stimuli, and produce smaller effect sizes. There are several possible reasons for the differences in findings produced by these measures, the first important difference is that the measures differ substantially, the IES-R is measuring DSM-IV PTSD and the CAPS-V measuring DSM-V symptomology. It may also be linked with the finding, discussed in Chapter 2, that self-report measures tend to produce inflated estimates of symptom severity as compared to the structured interview. The aim of a screening tool such as the IES-R is to be quick to administer and highly sensitive, which sacrifices the specificity gained from the structured interview. The finding is also consistent with results suggesting that different relationships were produced from psychopathy measures reported by Burley (2016). Despite a finding being reported from using the PCL-R clinician (or researcher) conducted assessment, the results from a self-report measure of psychopathic personality did not replicate the relationships found between pupil response and PCL-R factors. However, the difference was likely to be magnified in a psychopathy sample, as individuals are more likely to be motivated to conceal the undesirable personality traits associated with psychopathy. Overall, this comparison provides support for the validity of the construct being measured, support for

the validity of results through the ability to re-produce effects, and suggests that administration of the 'gold standard' instrument was an appropriate choice.

3.3.8.1.5 Overall Limitations

The cross-sectional experimental design appeared to reveal difference in individuals with PTSD. However, it is not clear as to whether this enhanced emotional reactivity was directly attributable to the state of PTSD, or whether this represented a pre-existing trait vulnerability to the disorder. This issue of the cross-sectional experimental design is considered further in the final discussion, Chapter Five, section 5.1.2.

The study sampling technique aimed to reduce the number of individuals taking high levels of psychotropic medication, as these may have complex effects on the autonomic nervous system and pupil response. However, this sample was not medication free, and individuals had varying histories of substance and alcohol use. Supplementary medication analyses are included in Appendix A and show that the main psychotropic medication in use were antidepressants. Research suggests that serotonin (5-HT) has an impact at the level of the iris, and that particular 5-HT receptor types are involved in relaxation of the sphincter of the pupil (Costagliola, Parmeggiani, Semeraro, & Sebastiani, 2008). This would suggest dilation after taking SSRI medication, which has been confirmed in studies of sertraline administration and pupil size (Saletu & Grünberger, 1988; Schmitt, Riedel, Vuurman, Kruizinga, & Ramaekers, 2002). Individuals being treated for depression also show reduced PLR compared to controls, which persists during and after treatment with SSRIs, when the individual is considered 'recovered' (Bär et al., 2004). Bär and colleagues suggest that medical treatment had a larger effect on autonomic function, as measured by the pupil light reflex (PLR), than the state of depression itself. Theofilopoulos, McDade, Szabadi and

Bradshaw (1995) reported the effect of non-SSRI antidepressants on pupil kinetics, and suggest that the amplitude of the PLR is consistently reduced under antidepressant versus placebo at all levels of light intensity. Supplementary analysis suggested that belonging to the high PTSD symptom group led to a reduction in the ICR, but there were no differences between individuals within the high symptom group who were taking medication, and those who were not. Individuals taking opiate medications were excluded entirely, as opiates can have a profound effect on resting pupil size and pupil kinetics, and previous preparatory work (see Appendix C) suggested general visual impairment and poor contrast sensitivity in individuals taking high doses of psychotropics and opiate pain killers.

3.3.8.2 Implications and Conclusions

These studies cannot isolate the specific mechanisms of autonomic activity which contribute to the apparent relationship between the ICR and emotional modulation and PSTD, but the theory behind the reduction in the ICR is in line with the literature suggesting reductions in parasympathetic regulation and/or increased activity of the sympathoadrenal axis are present in PTSD. Cross task comparisons indicate no abnormality in pupil dilation patterns to sound clips (see Appendix B, section 2.2.1) demonstrating that the pupils of the individuals with PTSD were not immobile, which would have produced a reduced ICR. The observation of normal pupil dilation response in contrast to an abnormal pupil constriction response suggests a constriction impairment, which is linked to reductions of activity in the parasympathetic nervous system. It is possible that the task employed was sensitive to baseline parasympathetic dysfunction reflected by the attenuated constriction, whilst lack of increased resting pupil diameter in contrast to the increased emotional modulation reflected suggested enhanced states of sympathetic activity, rather than an increased baseline level of

sympathetic activity. No gold-standard exists for the measurement or assessment of acute activation or chronic tonal change of the ANS. Instead, assessment and theory development rely on converging bodies of evidence, which the finding of dysfunctional autonomic responsivity in individuals with more PTSD symptoms add to. Overall, the literature utilising physiological assessment in PTSD has shown that abnormality in the ANS is associated with elevated rates of cardiovascular disease (for a review of cardiovascular disease in veterans and civilian samples see Coughlin, 2011) and an increasing risk of harm through heart attack and atherosclerosis in PTSD. The results of Experiment One suggest PTSD symptom severity to be related to a reduction in pupil constriction to light, and the results of Experiment Two suggest this abnormality was not associated with reduced pupil dilation. This finding provides support for reduced tonic parasympathetic activity, which is generally implicated in poor prognosis for heart disease (Nolan et al., 1992).

In future studies, the use of a pre-test post-test design measuring pupil activity before and after a treatment intervention for PTSD would provide a further powerful test of changes in pupillary function in PTSD, as would a multiple time point study assessing the relationships between pupil function and reduction in symptoms during the course of an intervention. Over all, this study showed that the use of pupillometry is sensitive to alterations in arousal that are hypothesised to occur due to mental illness, and demonstrated the utility of examining the full waveform of pupil activity, from resting baseline, to constriction, to re-dilation.

CHAPTER FOUR

4.1 Personality, Perceptual Sensitivity, and Post Traumatic Stress

"*We see the world in a particular way not because that's the way the world is, but because that's the way we are.*"

Snowden, Thompson, and Troscianko (2006, p3)

4.1.1 Abstract

This chapter presents a literature view of research relating perceptual sensitivity to personality; the origins of which can be traced back to Ivan Pavlov's studies in typology and individual differences in the nervous system, through to modern psychophysics and the assessment of visual contrast thresholds. Experiment Three builds on these bodies of literature to assess whether measures of visual contrast sensitivity can be utilised to detect alterations in arousal due to the presence of Post-Traumatic Stress Disorder, a disorder defined by chronic alterations in arousal and hypervigilance. The pilot work for this chapter was conducted in a highly medicated sample of secure hospital inpatients (see Appendix C) and findings revealed the potentially detrimental effects of high-levels of psychotropic medication use on contrast thresholds. The data presented in this chapter utilised an assessment of the visual contrast sensitivity function in a sample of community participants ($N = 67$); 19 with a diagnosis of PTSD, 22 who had experienced a traumatic event but did not meet diagnostic criteria, and 26 control participants who did not report a Criterion A trauma. Participants were assessed for PTSD diagnostic status using the CAPS-V, measures of PTSD symptom severity were also taken using the IES-R, and personality traits were measured using the Harm Avoidance Scale of the TCI. Results provide no evidence that individuals

with a categorical diagnosis of PTSD exhibited lower contrast detection thresholds in comparison to a the trauma-exposed control group. However, dimensional analyses of relationships between contrast thresholds and severity scores from PTSD subscales revealed differential effects of subscales on performance. Higher levels of avoidance were uniquely related to higher contrast thresholds, and higher levels of re-experiencing symptoms were related to reductions in the contrast threshold. Results are discussed in terms of the heterogenous nature of PTSD and the emotional dysregulation account of PTSD subscales proposed by Hopper, Frewen, van der Kolk and Lanius (2002).

4.1.2 Historic Perspectives on Personality and Perceptual Sensitivity

Experimental psychology and vision science make a distinction between 'bottom-up' and 'top-down' influences on visual perception. A standard explanation of the difference between these two influences on visual perception is bottom-up processing as direct data-driven or stimulus-driven processes, whereas top-down processing is influenced by expectations, existing knowledge, experiences, context, and so on (Eysenck, 1998). The difference is, therefore, suggested to lie in whether the information is optical and directly drawn from the stimulus, or non-optical and already existing within the system. The following review aims to determine the case and theory for a relationship between visual perception and a specific non-optical factor, personality.

The first half of the 19th century saw a boom in experimental psychological research relating personality types to individual differences in performance. A review provided by Granger (1953) summarised this research, with a specific focus on personality and visual

perception. Granger's review noted that science has been "forced to admit the influence of autistic and motivational factors, even at the level of 'pure' sensory research" (p.8). He believed that these visual processes are in fact markedly dependent on hereditary and constitutional factors. Granger comments on previous summaries in this area as lacking in scientific content, and also containing an undue amount of "verbiage and vague speculation" (p.34). The research reviewed had been undertaken within the frame work of Hans Eysenck's early research on personality dimensions (Eysenck, 1947). These initial dimensions were labelled extraversion and neuroticism, and perceptual studies focussed on distinguishing these personality 'types' via differences in performance on visual measures. The experimental population for the studies by Eysenck were often chosen on the basis that they were failing to adapt to army life, and subsequently referred to the emergency hospital by a psychiatrist and diagnosed as 'neurotic' (Eysenck, 1947). The term 'personality type' here refers mostly to conditions which require psychiatric intervention, rather than dimensional traits, making the research difficult to compare to modern equivalents. The research summarised by Granger appears to have been largely descriptive, atheoretical, and conducted in the absence of a predetermined hypothesis. For example, the existence of differences in visual performance between groups is often referred to, but neither the direction of the effect (whether it was better or worse) nor speculations as to the causality are referred to. There is no mention of a theory as to why individual variance in personality might relate to visual perception. The theoretical basis for a relationship between personality and perceptual sensitivity was yet to be discussed.

The idea that individual differences in personality are related to individual physiology has its origins in the work of the Russian physiologist, and later world famous experimental psychologist, Ivan Pavlov (1927). Although better known for his work on the conditioned

reflex, Pavlov developed his theory of personality, individual differences, and problems of typology through numerous studies of individual differences in the dog. Pavlov believed that individual nervous systems differ in their ability to tolerate stimulation, and their consequent differences in performance and response can provide an observable measure of these differences. Pavlov theorised that an individual's response magnitude increases with stimulus intensity up to a limiting point. At this point, the opposing process of 'transmarginal inhibition' replaces the response, so that when the magnitude of the stimulus increases the intensity of the excitatory process is also held to decrease (Gray, 1964). Pavlov's experimentation with dogs showed that individual animals could be classified by their "threshold of transmarginal (or protective) inhibition" (Gray, 1964, p. 161). The meaning behind the Russian word for transmarginal is, literally, "beyond the limit" (Gray, 1964 p. 161). This concept came to be the dimension of Pavlovian personality theory known as 'the strength of the nervous system'. Whilst strong nervous systems can maintain arousal when exposed to intense stimuli, Pavlov argued that weak nervous systems, when strongly stimulated, show a paradoxical reduction in size of response. Pavlov's theory of the relationship between personality and strength of the nervous system emphasised the negative aspects of the weak nervous system, such as susceptibility to exhaustion and the tendency for performance to deteriorate following a comparably lower point of optimal arousal. However, the theory was later expanded on by Teplov's laboratory (1960/1964), who hypothesised that this 'weakness' of the nervous system is owing to high reactivity, or sensitivity. According to Nebylitsyn, Rozhdestvenskaya, and Teplov (1960) there exists a negative correlation between sensitivity and strength of the nervous system, such that the weak nervous system will also be impelled into action by relatively weak stimuli (Nebylitsyn et al., 1960). In Pavlov's words,

"The strong nervous system acts as if it damped down to stimulation, while the weak nervous system acts as if it amplified to it" (in Gray, 1964, p. 289).

Much of the Russian work was unobtainable in English up to the late 1950s, and where translations did exist subtle differences in terminology limited their application to Western studies on personality. The ideas of Pavlov and those influenced by him were later to be brought into Western psychology by Hans Eysenck (1957) and Jeffrey Gray (1964). In 1964 Gray published the first volume in an international series on experimental psychology. *Pavlov's Typology* aimed to interpret the Russian theory of personality, and their attempts to apply Pavlovian personality theory to humans. Gray's translation of Pavlov's Typology made available a reinterpretation of the strength of the nervous system hypothesis in order for its practical integration into Western work. Gray provides a summary of evidence for weak and strong nervous systems' variation along the dimension of arousal, or "arousability" (Gray, 1964, p. 290), see Figure 18 for an illustration of this relationship.

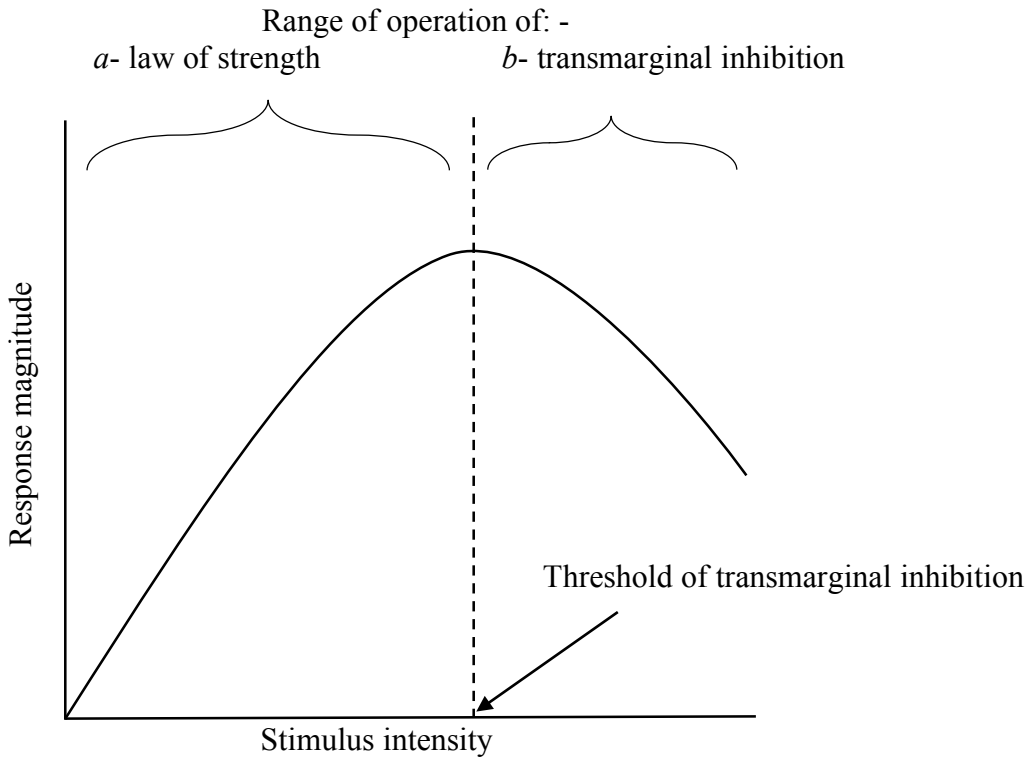

Figure 18. An individual arousal and performance function. The dashed line represents the threshold of transmarginal or protective inhibition. Adapted from p. 162 of Gray, 1964.

Western psychologists built on the work of the Russian school and the concept of arousability by speculating that strength of the nervous system may correspond to personality traits, including levels of extroversion and/or levels of neuroticism (Eysenck, 1957; Eysenck, 1967; Gray, 1967; Frigon, 1976). In this model, the relationship between perceptual sensitivity and personality dimensions is mediated by strength of the nervous system. Therefore, a person with a 'weak' nervous system (i.e., one that is sensitive to weak stimuli, easily aroused, and therefore, presumably, oversensitive to or exhausted by strong stimuli) is more likely to be neurotic and introverted. Thus, the basic tenet and testable hypothesis of

Western research on personality and perceptual sensitivity is that those with a weak nervous system, as defined by these personality constructs, will also have lower sensory thresholds for detecting stimuli.

Russian methods of assessing the relationship between sensory sensitivity and strength of the nervous system involved determining the 'threshold of appearance' for a speck of light on a dark background following a period of dark adaptation. This value was then combined with the 'threshold of disappearance' and averaged. This method asks participants to say when they see the speck of light on a dark background in a 'yes/no' discrimination paradigm to ascertain visual sensitivity. The researchers would then assess the effects of caffeine on these detection thresholds, based on the notion that different nervous systems would interact with caffeine (Nebylitsyn et al., 1960). There is some evidence to suggest that this hypothesis has been examined outside of soviet groups. Gupta and Nicholson (1985) investigated simple visual reaction time, personality, and strength of the nervous system and concluded that they had found a significant relationship between neuroticism and weakness of the nervous system, as measured by visual sensitivity. Gupta and Nicholson recruited participants who scored highly on the neuroticism scale of Eysenck's Personality Inventory (EPI; Eysenck & Eysenck, (1964)) and assessed whether neurotic subjects reacted faster to the appearance of a simple visual target for a range of stimulus intensities, coupled with a signal detection task for a bright light. Their results indicate that between the two highest intensities of stimuli (light level) low neurotic subjects show a continued linear increase in reaction speed, whereas high neurotic subjects show a decrease in speed. This decrease is consistent with what would be expected with an individual having passed a point of optimum performance. However, they did acknowledge that there might be an explanation other than lower detection thresholds for these results and provided a study on

reaction time to assess this limitation. It is possible that the effect is due to a change in the criterion the person uses as a basis for when to respond, reflecting a response bias rather than a change in the sensitivity of the sensory processes. This would result in an effect of personality on the dependent variable when in fact the two groups may have had the exact same sensory perceptual experience. Indeed, the second study did reveal that individuals high in neurotic traits presented with more false alarms, but the authors state that this did not affect their conclusions once controlled for statistically. Gupta and Nicholson (1987) provided a second study to address an alternate, but complementary, hypothesis. Here the concepts of arousal and sensitivity of the nervous system are incorporated into a theory of 'vigilance'. The authors note the significant role of arousal in performance, noting a drop-off in performance with time, or 'vigilance decrement' which is consistent with a decline in performance with task time and time of day effects. However, there was no significant effect of personality on vigilance 'decrement', i.e. 'personality' (neuroticism) was not associated with the point at which individual performance declines. Gupta and Nicholson conclude that they may not have used the most suitable test for the 'arousal/ sensitivity' model of personality.

This line of research was not conducted without criticism. Pavlov himself had been condemned as guilty of over-simplifying an extraordinarily complex subject (Fulton, 1936). The personality psychologist, Gordon Allport, regarded tests of simple sensory and perceptual processes as having little value to the study of personality. In Allport's words, simple visual tests are "… too trivial to tap the developed volitional functions of personality. Adaptation to light or darkness, for example, is primarily a retinal characteristic and bears but a tenuous relation, if any at all, to personality" (Allport, 1937, p. 438). As can be seen from the research already reviewed, the majority, if not all, of these studies, assessed visual

sensitivity via detection of light in a dark room following a period of dark adaptation. Their aim appears to have been to see whether strength of the nervous system impacts on the minimum energy required for a simple visual effect to 'appear' to participants. A note should be made here that Pavlovian 'neurology' does not correspond to anything that the contemporary neuroscientist would recognise. This fact has been recognised by Hebb (1955) who suggested that the term Central Nervous System (CNS) be renamed the 'conceptual nervous system' (cns), a phrase which was later adopted by Jeffrey Gray. Although it may be the case that too much emphasis cannot be placed on the neuroscience behind these concepts, previous outcome measures have all largely involved the photoreceptors of the eye, namely the rods and cones. In line with Allport's critique that this is a primarily retinal characteristic these photoreceptors contain photo sensitive pigment, and predominantly absorb light (Yau, 1994). Although the cns does stand for 'conceptual' it is unlikely that such a peripheral measure of light absorption could be related to personality. A more central outcome measure would involve a task that has been demonstrated to be mediated and limited by the visual cortex, such as contrast sensitivity (Avidan et al., 2002). Avidan et al. used fMRI to and presentations of simple line drawings to demonstrate that early visual areas (V1) are strongly contrast dependent, whereas there is contrast invaraince in higher visual areas (the lateral occipital complex), which represent more complex perceptual experience.

4.1.3 Contrast Sensitivity

Modern research is now able to measure contrast sensitivity quickly and easily (Pelli & Bex, 2013) and rather than comprising separate areas of study, the influence of non-optical factors, such as arousal and emotion, in visual perception are now relatively well established in psychological research. Visual contrast refers to the representation of the borders or edges

of an object through a light-to-dark transition (Owsley, 2003) and assessments of this ability can be used to define individual thresholds between what is visible and invisible (Pelli & Bex, 2013). Contrast is expressed as a percentage between 0% and 100%. At 0%, there is no physical edge between the neighbouring objects. A physical edge exists for any contrast value greater than 0, but whether or not this edge is perceptible is dependent on the image processing capabilities of the observer. Threshold refers to the value of contrast the observer requires to see the target reliably. The reciprocal of threshold is called sensitivity. Both threshold and sensitivity are conventionally expressed on Logarithmic (base 10) scale. A contrast threshold of 1% (0.01) is a log contrast of - 2.0. As the reciprocal, contrast sensitivity would be 100 and expressed logarithmically as 2.0. Figure 19 represents varying letter contrast, illustrating that the target letter becomes more difficult to see as you reduce percentage contrast toward zero. Although contrast sensitivity represents a dimension of vision which is largely separable from visual acuity, the spatial frequency of the object is also represented in the full contrast sensitivity function. Spatial frequency is measured in cycles per degree of visual angle, with more cycles per degree representing higher spatial frequencies and requiring higher visual acuity. In assessments of letter sensitivity, spatial frequency is represented by the scale of the letter. A plot of sensitivity across a range of spatial frequencies forms the contrast sensitivity function.

Figure 19. Varying percentage contrast for a digitally band pass filtered Sloan letter 'C'.

Individual contrast threshold can be estimated by a variety of psychophysical techniques including detection (indicate when you see a stimulus), discrimination (indicate whether stimuli are the same, or different), recognition (indicate whether you have seen a stimulus before) and identification (what is the stimulus) (Owsley, 2003). Research has shown that, despite the apparent objectivity of these assessments, there is variation within some methods due to the subject's own strategy and criterion (Sekuler & Hutman, 1980; Vaegan & Halliday, 1982). This was also suggested as a criticism of the early Russian studies, as the intended predictor variable, neurotic personality, interfered with the criterion variable in discrimination studies (Gupta & Nicholson, 1985; Nebylitsyn et al., 1960). Most psychophysicists therefore use a 'forced-choice' paradigm where a stimulus is always presented and the observer must choose one of two (or more) alternatives about the nature of the stimulus (e.g., was it presented to the left or right of fixation). Alternate forced choice

identification paradigms appear to have higher test-retest reliability, as they are not subject to personality variables and internal criteria for reporting the presence of the stimulus.

Methods of assessment for contrast sensitivity have advanced more recently so that the full contrast sensitivity function (CSF) can be estimated using prior knowledge of the CSF to maximise information gain in a minimal number of trials (Lesmes, Jeon, Lu, & Dosher, 2006; Lesmes, Lu, Baek, & Albright, 2010; Pelli & Bex, 2013; Vul, Bergsma, & MacLeod, 2010). Lesmes et al. (2010) demonstrate excellent agreement with independent contrast threshold estimates using 100 trials (approximately 10 minutes) and that only 25 trials were required to estimate sensitivity through the area under the log CSF. Hou et al (2016) demonstrate that these assessments are appropriate for use at the individual and group level. Lesmes, Wallis, Jackson and Bex (2013) demonstrate reliability of the measure in as little as 15 trials. Pelli and Bex (2013) suggest that the quick CSF provides a method to reduce precious time in assessing clinical samples.

4.1.4 Contrast Sensitivity and Arousal

Over the past ten years, research employing the assessment of contrast sensitivity to investigate relationships with non-optical variables has confined its self to state measures, such as emotion, rather than trait measures, such as personality. A relationship between emotion and visual sensitivity is interesting in relation to the breakdown and supposed characteristics of the particular personality type of ‘neuroticism’. Eysenck (e.g. 1967) treats the dimension of neuroticism as equivalent to ‘emotionality’, or the tendency to experience strong emotions. These studies hold the experimental advantage that emotional state is open

to experimental manipulation, whereas personality quite clearly is not. Emotional arousal or emotionality may, therefore, provide a mediating link between personality and perceptual sensitivity. The first study to demonstrate a direct relationship between emotion and basic vision was reported by Phelps, Ling and Carrasco (2006). Phelps et al. showed that emotion, namely the brief presentation of a fearful face, potentiated the visual sensitivity as assessed by a visual contrast sensitivity test. The authors found that the visual detection threshold for gabor patches improved after this fearful threat cue. Zadra and Clore (2011) suggest that emotion routinely affects how we see, and describe how different emotion states have been shown to act on perception. Fear, as shown by Phelps et al. (2006), can affect low-level visual processes, moods can alter our perception of the steepness of a hill (Riener, Stefanucci, Proffitt, & Clore, 2011), and goal-directed desires can change the apparent size of goal-relevant objects (Bruner & Goodman, 1947). It is noteworthy that the only studies on basic visual perception tend to include fear and negative arousal. A recent research project by Woods, Philbeck, and Wirtz (2013) looked at the consequences of hyper-arousal for human vision. The authors used a pre-test post-test repeated measures design, and manipulated arousal via a 50 second cold pressor stimulation task (submerging a hand in 0-2 degree water) versus a sham task in which water was at room temperature. The authors found lower thresholds for visual contrast detection in the cold pressor stimulation group alone. Along similar lines, Lee, Baek, Lu, and Mather (2014) show how arousal modulates the whole contrast sensitivity function within a fear conditioning paradigm. Their results suggest that induced arousal in the experimental paradigm, as measured by skin conductance, resulted in a shift in peak contrast sensitivity to lower spatial frequencies, along with an increase in the bandwidth of the spatial frequency function. This fits with existing evidence suggesting that the neural response of the amygdala to fearful expressions is greater for intact or low-

frequency faces than for high-frequency faces (Vuilleumier, Armony, Driver, & Dolan, 2003). There appears to be strong evidence for an effect of arousal and emotion on the basic visual property of contrast sensitivity, but as of yet there are no studies relating contrast sensitivity to typology.

To conclude, this review has highlighted the importance of theory in research relating to personality. As discussed by Corr and Perkins (2006) it is obvious that, at least in the field of personality, much research is still atheoretical, relying upon data-driven strategies. The review has also suggested that there exists no research employing modern visual contrast sensitivity techniques in the domain of personality. Current research appears to have made the move to assessing state measures, such as emotion and arousal. There is a definite lack of research around trait relationships between visual threshold and personality. Points that have yet to be clarified include whether arousal (positively or negatively valenced) can improve basic vision, or whether this is limited to negative arousal as is synonymous with negative emotions or defensive reactions to threat.

4.1.5 Contrast Sensitivity and Post-Traumatic Stress Disorder

Research into sensory thresholds in schizophrenia is well developed, but findings conflict as to whether schizophrenia is associated with visual contrast deficits or sensitivity. Kiss, Fábián, Ágnes and György (2010) found reductions in contrast thresholds to be associated with levels of anomalous perceptual experiences (e.g. visual hallucinations) in un-medicated, first episode schizophrenia. They suggest that increased visual sensitivity may be a mechanism through which perceptual anomalies, such as hallucinations, occur. However,

Slaghuis (2004) found reductions in visual contrast sensitivity using both static and temporal contrast detection paradigms. Skottun and Skoyles (2007) reviewed evidence of visual contrast detection in schizophrenia and conclude that attentional deficits may account for poor performance, and that the evidence for a magnocellular deficiency is limited. Chen and colleagues (2003) suggest another confound of this research lies in the use of anti-psychotic medications used to control symptoms. Antipsychotics, particularly first generation 'typical' antipsychotics, have been found to increase the contrast threshold (see Appendix A for a review of the effects of psychotropic medication on basic vision and Appendix C for experimental data regarding psychotropic medication and visual contrast). The mechanism for this effect is suggested to lie within the dopaminergic system, with pharmacotherapy for schizophrenia blocking dopamine post-synaptic receptor sites (Chen et al., 2003). When assessing detection thresholds of individuals with schizophrenia who were not taking medication, Chen et al. found evidence for visual thresholds that were significantly below controls, a finding that the study of Kiss et al. supported.

Despite a central role in theoretical accounts of clinical trauma syndromes, there is surprisingly little objective empirical evidence for heightened sensory sensitivity in individuals with the disorder, and its role seems to rely on the subjective self-report of this heightened sensitivity. One line of evidence provides indirect support for this notion. Paige, Reid, Allen and Newton (1990) measured event-related brain potentials (ERPs) while playing tones of varying intensity to assess the evidence for 'sensory overload' in Vietnam veterans with and without PTSD. As an auditory stimulus grows louder a particular component of the evoked potential to the stimulus (P200) also grows larger. However, at louder levels this reverses and the response becomes smaller. The authors found the veterans with PTSD (n = 9) demonstrated reduced ERP responses in comparison to controls (n = 5). Reduced ERP

responses reflect a protectively tuned sensory system, that attempts to shut out increased stimulation. Hence, a state protective inhibition. This state of protective inhibition is active as individuals with PTSD are more "autonomically arousable" (p. 419) than individuals who are not traumatised. Abnormal stimulus response intensity functions have also been noted in PTSD by Lewine et al. (2002) using auditory tones and the P200 ERP. The authors suggest that this indicates an adaptive mechanism, and "these subjects live in a state of persistent over arousal" (Lewine et al., 2002, p.1690). Hendler et al. (2003) conducted an fMRI study to assess sensory processing of trauma-related scenes in the visual cortex and the amygdala. They recruited 20 combat veterans, 10 with PTSD and 10 without. The authors demonstrate increased activation of the visual cortex in PTSD positive individuals while viewing backward masked images (below the recognition threshold) along with increased activation of the amygdala, regardless of recognition threshold. The finding of increased activation in the visual cortex is in line with studies suggesting that emotional content modulates activation in this region (see; Lane, Chua, & Dolan, 1999; Lang et al., 1998). Thus, the extant evidence seems to show that patients with PTSD show a pattern of data that suggests that they are more stimulated by sensory stimuli. However, there appears little evidence that they actually show greater sensitivity (e.g., lower thresholds for detecting a stimulus) for stimuli in any sensory modality. A review of the research literature suggests that this is due to a paucity of such studies, rather than a genuine lack of effect. Hence, the aim of the current study is to use psychophysical techniques to measure sensitivity to visual stimuli with the hypothesis that individuals with PTSD will have lower visual thresholds than controls.

4.1.6 Methods

4.1.6.1 Sample and Exclusions

The sample comprised the individuals described in chapter two, with the addition of fourteen further control subjects who had not experienced a Criterion A traumatic event. These individuals were recruited through preparatory work which is described in Appendix C. Individuals were excluded if they reported a history of visual problems, or required glasses which they did not bring to the testing session. Three individuals were excluded due to extreme outlying variables in the log contrast threshold measure (extremely poor values). Histograms showed normally distributed variables and the Shapiro-Wilk assessment for normality was non-significant. There was no significant difference in ages between the groups (p = .481) and age was not significantly related to the contrast threshold outcome variable (r = .07, p = .57), therefore age has not been used as a covariate. Key demographics are displayed in Table 16 below.

Table 16. *Age, Gender and IQ Demographics for Experiment Three*

	PTSD Positive (n = 19)	PTSD Negative (n = 22)	Control (n = 26)	Internal consistency
Age	38.44 (*10.03)*	44.32 *(14.85)*	41.60 *(14.62)*	
Gender	48% female	38% female	47% female	
IQ	102.60 *(20.10)*	104.41 *(18.60)*	108.00 (*18.67)*	
CAPS-V	42.24 *(13.85)*	7.38 (*8.62)*	-	.95
IES-R	55.67 *(15.36)*	17.67 *(19.34)*	11.07 *(17.40)*	.97

Note. Mean *(Standard deviation)*. Internal consistency assessed with Cronbach's alpha.

4.1.6.2 Materials

The psychometric measures are described in Chapter 2. Visual contrast sensitivity was measured with the quick Contrast Sensitivity Function method (qCSF; Dorr, Lesmes, Lu, & Bex, 2013) with software designed by Peter Bex (2014). The software was obtained for use within this thesis with permission from the author and is also reported in Dorr et al., (2017). The task was presented using a laptop device (15.5" Apple MacBook Pro with NVIDIA GeForce GT 750M graphics card) running MATLAB 2014a with curve fitting and statistics extensions, the Psychophysics Toolbox (Brainard, 1997) version 3.0.11, and the FAST toolbox (Functional Adaptive Staircase Technique, FAST; Vul & MacLeod, 2010). The dimensions of the task on the screen was 1920 x 1080 pixels with a 60Hz refresh rate. The software runs a task to measure the contrast sensitivity function for identification of digitally band pass filtered Sloan letters (see Figure 19 for an example). The program uses Bayesian adaptive procedure to adjust contrast and spatial frequency that accelerates estimation of a full contrast sensitivity function defined by three parameters that describe peak frequency, peak sensitivity and bandwidth. The parameter used in the following analyses was the contrast sensitivity at the peak spatial frequency. This threshold estimate is based on the maximum sensitivity for the spatial frequency at which the individual performs the best (i.e. at which ever letter size the individual can see the lowest level of contrast). See Figure 20 for an individual performance graph, where this measure is represented by the peak of the curve.

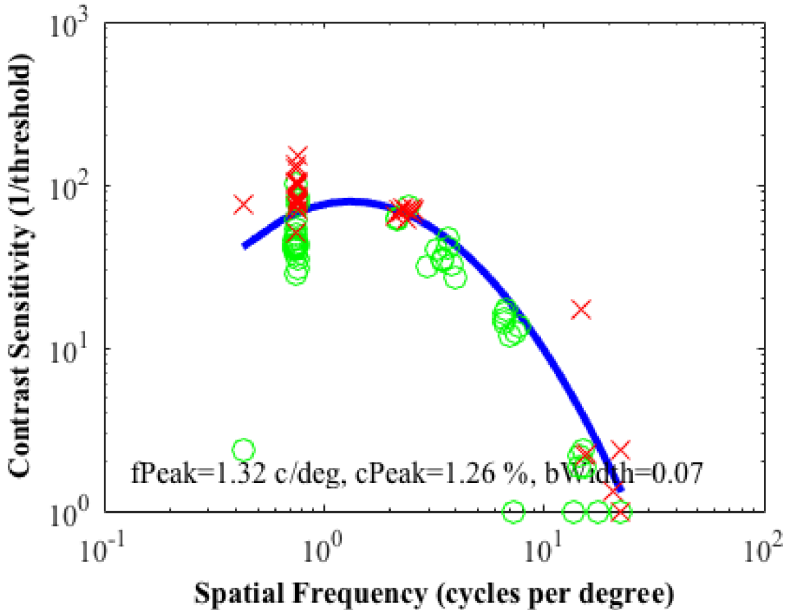

Figure 20. Example quick contrast sensitivity function displaying 3-parameter fit 100 trial contrast sensitivity function curve for the performance for one individual. Green circles represent correct responses and red crosses incorrect responses. fPeak = peak spatial frequency, cPeak = contrast sensitivity at peak frequency, bWidth = bandwidth.

Each trial was preceded by white markers that indicated the scale (spatial frequency) of the upcoming stimulus and framed the location of letter to engage attention. Stimuli were then presented in this location for 250 ms. Letters of the English alphabet were chosen for presentation by the program at random, representing a 26-alternate forced choice procedure. The use of 26 letters means that there is a very low probability of making a correct guess by chance. The participant was asked to respond verbally when they saw a letter, or to say pass when they could not see. An experimental session consisted of 20 practice trials, which were not scored, followed by 100 experimental trials (Lesmes et al., 2010) which formed the CSF estimates. The outcome variable was contrast threshold at the peak spatial frequency. Numbers closer to zero represent lower thresholds and better contrast sensitivity. In preparatory work, test re-test reliability was shown to be good for this measure in psychiatric

inpatients, over a re-test interval of 7 days (see Appendix C, section 3.4.6). Reliability is also documented in Dorr et al. (2017).

4.1.7 Results

4.1.7.1 Categorical Analyses of PTSD Status and Contrast Thresholds

A one-way analysis of variance (ANOVA) was conducted to examine the effect of PTSD status on contrast thresholds. There was a marginally significant effect of PTSD status $F(2, 64) = 2.89$, $p = .061$, $\eta 2 = .083$. Follow up planned comparisons revealed no difference between PTSD positive ($M = 0.1122$, $SD = 0.0043$) and PTSD negative ($M = 0.1124$, $SD = 0.0026$) groups. There was a significant[13] difference between the control group ($M = 0.1133$, $SD = 0.0032$) and the PTSD positive group ($p = .051$, $d = 0.29$) and the control and PTSD negative group ($p = .041$, $d = 0.31$) with small effect sizes. This suggests slightly poorer performance in the control group. The thresholds are illustrated in Figure 21 below and demonstrate that the range of scores in the PTSD positive group indicated the highest levels of performance, although this was led by three scores and not reflected in the means.

[13] Non-significant if applying Bonferroni correction for multiple comparisons ($p > .025$)

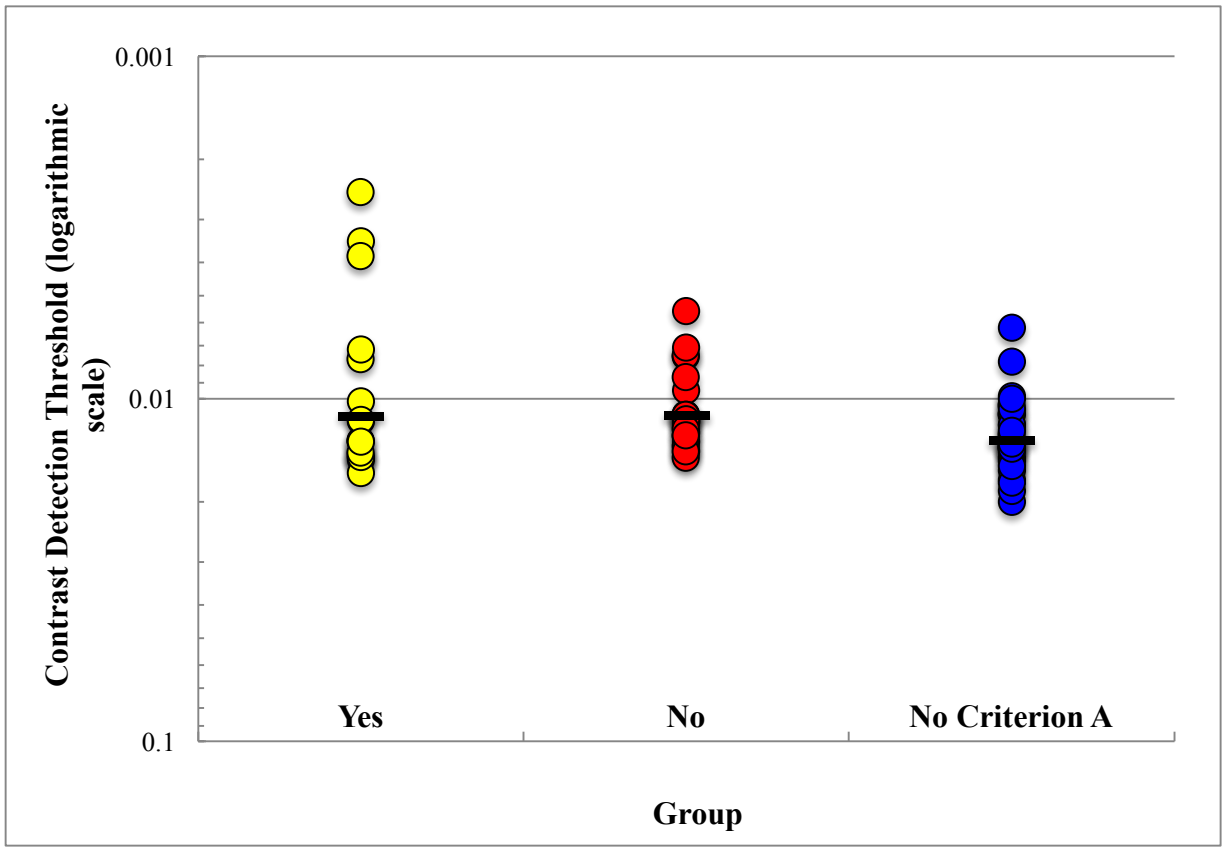

Figure 21. Contrast detection threshold as a function of PTSD status. Values closer to zero represent lower thresholds and greater perceptual sensitivity.

Table 17. *Zero-order Correlations Between PTSD Severity, Total Anxiety, Medication and Contrast Threshold within the sample (N = 67 for measures not using the CAPS, n = 41 for CAPS measures).*

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1. Contrast Threshold	-												
2. PTSD Severity CAPS-V	-.01	-											
3. PTSD Severity IES-R	-.29*	.88**	-										
4. Harm Avoidance	-.01	.71**	.71**	-									
5. Anxiety	-.05	.62**	.61**	.66**	-								
6. CAPS B	-.13	.90**	.88**	.64**	.51**	-							
7 CAPS C	.24	.79**	.67**	.56**	.55**	.67**	-						
8 CAPS D	.01	.94**	.81**	.68**	.62**	.77**	.75**	-					
9 CAPS E	-.12	.89**	.74**	.58**	.52**	.75**	.55**	.75**	-				
10. Age	.07	-.15	-.03	.00	-.35**	.03	-.28	-.15	-.20				
11. Medication score	.11	.43**	.43**	.48**	.49**	.43**	.43**	.40**	.27	.09			
12. IES-R Intrusion	-.25*	.80**	.92**	.64**	.54**	.88**	.56**	.72**	.65**	.06	.40**		
13. IES-R Avoidance	-.18	.76**	.91**	.64**	.61**	.70**	.73**	.74**	.57**	-.16	.38**	.75**	
14. IES-R Arousal	-.31*	.81**	.92**	.67**	.52**	.80**	.51**	.70**	.77**	.02	.42**	.81**	.75**

Note. * $p \leq 0.05$, ** $p \leq 0.01$

Table 18. *Regression Statistics Examining Relationships Between CAPS-V PTSD Symptom Scales and Contrast Thresholds in the Trauma Sample (n = 41).*

	B: Re-experiencing			C: Avoidance			D: Cognition and Mood			E: Arousal and Reactivity			
Criterion Variable	β	*t*	Unique sr^2	β	*t*	Unique sr^2	β	*t*	Unique sr^2	β	*t*	Unique sr^2	R^2 *p*
Contrast Threshold	-.44	-1.80[a]	.07	.49	2.06*	.11	.22	0.74	.01	-.22	-0.89	.02	.22 .055

Note. PTSD symptom severity assessed by the CAPS-V. β = standardised Beta. Unique sr^2 = the semi partial correlation (squared) representing unique variance. [a] $p = .081$ * $p \leq 0.05$, ** $p \leq 0.01$.

Table 19. *Regression Statistics Examining Relationships Between IES-R PTSD Symptom Scales and the Contrast Threshold in the Trauma Sample (n = 41).*

	Intrusion			Avoidance			Hyper Arousal			
Criterion Variable	β	*t*	Unique sr^2	β	*t*	Unique sr^2	β	*t*	Unique sr^2	R^2 *p*
Contrast Threshold	-.06	-.28	.00	.14	0.74	.01	-.36	-1.65	.04	.10 .081

Note. PTSD symptom severity assessed by the IES-R. β = standardised Beta. Unique sr^2 = the semi partial correlation (squared) representing unique variance. * $p \leq 0.05$, ** $p \leq 0.01$.

4.1.7.2 Dimensional Analysis of Symptom Severity and Contrast Thresholds

The zero-order correlations, displayed in Table 17, showed that PTSD total symptom severity assessed using the CAPS-V was not significantly related to contrast detection thresholds. However, some non-significant trends were revealed through analysis of correlations between the CAPS-V subscale scores and the detection threshold. There was a trend for better performance with higher levels of intrusive and hyper-arousal symptoms, and poorer performance with increasing levels of avoidant symptoms.

Linear multiple regression analyses were conducted to assess the unique contributions of PTSD subscales to the contrast threshold. Assumptions of multiple regression were satisfied; VIF did not indicate multi-collinearity or redundancy in predictor variables (VIF 2.64 – 3.42), Mahalanobis distance values indicated no multivariate outliers, and assumptions of normally distributed residuals were satisfied through inspection of P-P plots.

The regressions revealed differential effects of subscales on detection thresholds, consistent with the zero-order trends. There was a marginally significant effect of CAPS-V subscale B, 're-experiencing', accounting for 7% of the unique variance in contrast threshold. This indicated slightly better performance with higher re-experiencing subscale scores. The opposite effect was observed for the avoidance subscale C, which accounted for 11% of the unique variance in contrast threshold. This suggested that higher levels of avoidant symptoms were related to poorer contrast detection thresholds. Use of the full CAPS-V symptom severity score obscured this relationship.

The zero-order correlations also revealed a significant negative relationship between IES-R score and contrast detection threshold, suggesting higher IES-R scores to be related to lower detection thresholds. This finding was contrary to use of the full CAPS-V symptom

severity score, and analysis of subscale correlations revealed a pattern consistent with the findings from the CAPS, but with no unique significant values. The significance of the full scale IES-R administration was not obscured by conflicting subscales, possibly due to the absence of Criterion D and re-organisation of PTSD symptom factors between DSM-IV and DSM-V. A multiple regression assessing the unique contribution of the IES-R subscales (intrusion, avoidance and arousal) revealed no significant unique contribution of any IES-R subscale (see Table 19).

The hypothesised relationship between a 'sensitive' personality, as assessed through the Harm Avoidance (HA) scale of the Temperament and Character Inventory (TCI; see Chapter 2 for details of this measure) was not supported in the full sample, despite the large relationship between HA scores and PTSD symptom severity.

4.1.8 Discussion

The hypothesis that individuals with a diagnosis of PTSD would have lower contrast detection thresholds and thus demonstrate greater perceptual sensitivity was assessed. This categorical hypothesis was not statistically significant, when comparing individuals with and without PTSD that had been exposed to a trauma, but the range of thresholds indicated that individuals with the lowest contrast thresholds belonged to the PTSD positive group. Multi-dimensional analysis using the CAPS-V measure painted a more complex picture than the categorical analysis could reveal, as there was a differential effect of subscales. The re-experiencing subscale of the CAPS-V was uniquely related to lower detection threshold, and the avoidance subscale was associated with increases in threshold. This pattern of trends was

replicated in the correlational subscale analysis using the self-report IES-R, but the subscales did not uniquely contribute in the regression. This may be because the effect of IES-R total severity score was significant in capturing this association, an effect which was also found within Experiment One. The similarities in the findings produced from using two measures are a strength, which increase the construct validity of PTSD measurement. However, differences may be attributable to the fact that the IES-R captures DSM-IV PTSD symptoms, whereas the CAPS is an assessment of DSM-V symptomology. The Criterion D variable, alterations in mood and cognition, which was new to DSM-V, showed no significant relationships and may have reduced the predictive power of the CAPS-V total severity scale.

The opposing relationships observed for both re-experiencing versus avoidance are interesting. However, the finding is difficult to interpret within a body of existing literature, as there are no existing studies of PTSD and contrast perception thresholds. In addition, most studies of physiological arousal and PTSD are categorical in their assessment of PTSD. Many studies also use trauma-driven scripts as a mechanism to induce state arousal, assessing a modulated response, rather than measuring baseline or 'trait' levels as was the aim herein. Andrews, Troop, Joseph, Hiskey and Coyne (2002) suggest that individuals vary with regards to whether avoidant strategies are successful in reducing arousal, and found successful avoidance to reduce distress. Reduced sensitivity with higher levels of avoidance might reflect a 'successful' strategy. Longitudinal studies (Scheeringa et al., 2005) have also shown reductions in re-experiencing over time versus increases in avoidance, indicating that this may be a commonly employed 'strategy' to reduce distress over the long term. Indirect evidence of the effect of differential symptom combinations and physiological arousal can provide some indirect assistance in interpreting this finding. Reductions in arousal have been associated with a dissociative subtype in PTSD. For example, in study of physiological

reactivity in rape victims, Griffin, Resick and Mechanic (1997) suggested lower physiological arousal and suppression of physiological responding is associated higher peritraumatic (at the time of the trauma) dissociation scores[14]. The finding of higher re-experiencing scores being related to lower thresholds and a consistent trend for the hyper-arousal scale can be interpreted within the literature on the visual effects of flashbacks. Although, again, a caveat to this is that most studies use state measures of flashbacks. Neuroscience research strongly implicates a role for the amygdala in re-experiencing and hyper-arousal (see Weston, 2014 for a review of biological evidence and theoretical model of hyper-arousal), with a multifunctional impact on other brain regions, including the visual cortex. Visual perception is suggested to be more sensitive in PTSD, as evidenced by attentional studies assessing perceptual biases for trauma-related stimuli (Kleim et al., 2012). fMRI studies indicate that the neural basis for the experience of visual flashbacks recruits the early visual cortex. Whalley et al. (2013) found that, compared with ordinary episodic memory which recruited the medial temporal lobe, the experience of flash backs was associated with increased activity in the sensory and motor areas.

Hooper, Frewen, van der Kolk and Lanius (2007) assessed the neural correlates of PTSD in relation to symptom dimensions to reveal potential differential neural substrates; an approach which a categorical diagnostic approach would be unable to achieve. The authors suggest that a dimension of emotional 'engagement' is associated with symptom dimensions of re-experiencing, avoidance and dissociation. Re-experiencing represents the high end of over-engagement and dissociation represents under-engagement. In their model, the avoidant symptom dimension represented a lower level of engagement than re-experiencing. However,

[14] In the current sample, only one individual reported dissociative symptoms, and within the CAPS-V this is considered as a subtype diagnosis, so scores are not included in either the total score or subscales.

the authors also note the complexity of the symptom dimensions in PTSD, where different symptoms involve simultaneous or rapid sequential unfolding types of psychobiological responses. The current study involved no manipulation of state, as it aimed to address trait sensitivity. It is possible that the symptoms of over arousal in PTSD are not wholly amenable to measurement in resting state studies. Although, weak but significant effect sizes have been found in resting state studies using heart rate (r = .18) and skin conductance (r = .08) studies (see Pole, 2007).

4.1.8.1 Limitations

This study included twenty-three individuals taking psychotropic medications. However, supplementary analysis reported in section 1.8.3 suggests there was no significant difference in threshold between medicated and unmedicated participants. The preparatory work recruited a sample of highly medicated individuals and found higher thresholds in individuals taking antipsychotic and opiate medication combinations (see Figure C25).

A further confound is depressive symptoms. Depression symptoms or co-morbid clinical depression was not isolated for assessment within these studies, but depression and PTSD are often co-morbid, with individuals with depression reporting more impairment and distress (Campbell et al., 2007). Studies assessing contrast threshold in subjects with depression demonstrate higher visual thresholds (Fam, Rush, Haaland, Barbier, & Luu, 2013). Lower retinal contrast gain has also been found, regardless of medication status, in a sample of 40 individuals with major depressive disorder (Bubl, Kern, Ebert, Bach, & Tebartz van Elst, 2010). However, a study of seasonal affective disorder (SAD) and clinical depression suggested greater sensitivity and enhanced contrast detection in clinical

depression (Wesner & Tan, 2006). The findings in this area of the literature are mixed, but depressive symptoms could have been a confound in the present study.

Finally, despite the hypothesised relationship between a sensitive personality and PTSD, there was no relationship or trend between levels of harm avoidance and contrast thresholds. Due to the small effect sizes, it is possible that a much larger sample would be required to detect an effect of personality on visual thresholds or, it is possible that, due to numerous other strong influences on visual thresholds, the effect size is too minute to detect.

4.1.8.2 Conclusions and Implications

There is currently a paucity of studies assessing hypothesised perceptual and sensory sensitivity in PTSD, and this study was the first to assess contrast thresholds in PTSD. Findings demonstrate the utility of using a multi-dimensional assessment of symptoms in PTSD to assess effects of specific symptoms on performance. Re-experiencing and hyper-arousal symptoms were suggested to be related to increased contrast sensitivity, whereas avoidant symptoms were related to reduced sensitivity. This complexity and heterogeneity within PTSD diagnosis may have contributed to the non-significant effect of PTSD diagnostic status on contrast thresholds, which has practical and theoretical implications for future studies. This study was limited by the potential confounds of depression and psychotropic medication use. Although the effect of medication was non-significant, the levels of interference due to psychotropic medications and their widely prevalent use to reduce symptoms suggest that this measure may not be the most practical to administer for symptom assessment in clinical practice.

CHAPTER FIVE

5.1 General Discussion

5.1.1 Summary

This thesis aimed to assess physiological hyper-arousal in post-traumatic stress disorder using pupillometry and assessment of visual contrast thresholds. Overall, the results suggested that pupillometry to emotive images is a promising assessment method, revealing enhanced state arousal to emotive images. The increased modulation due to positive images suggested that the hypothesised sensitivity was not limited to threat stimuli, although, the largest effect sizes were observed in threatening images. Studies of PTSD rarely use either positive or sad control conditions and, despite anecdotal evidence, no studies to date have explored enhanced sensory sensitivity in PTSD. Assessment of the full pupil response waveform was also novel within PTSD. Contrary to anecdotal accounts, this revealed no difference in the resting pupil size of individuals with PTSD, but did show a baseline autonomic deficit in the constriction reflex to light in individuals with PTSD. This was suggested to reflect a tonic imbalance in the parasympathetic nervous system, which studies of other mental disorders have also found. Although heightened arousal to emotive sounds was not supported, this was not suggested to represent a modality-specific sensitivity limited to emotive images, but was suggested to be due to differences in the experimental sounds paradigm. Within the assessment of sensory sensitivity in PTSD, a multi-dimensional analysis to inspect the CAPS-V subscales painted a more complex picture than the categorical analysis could reveal, as there was a differential effect of subscales. The re-experiencing subscale of the CAPS-V was uniquely related to lower detection threshold, and the avoidance subscale was associated with increases in threshold.

The following discussion considers the contributions of the thesis as a whole, with consideration of the experimental design and theory of PTSD, analysis methods (dimensional versus categorical exploration), implications, and overall limitations. Suggestions and recommendations for future study are included throughout the following sections.

5.1.2 Design and Theoretical Implications

The design of the studies conducted herein was cross sectional, sampling individuals at one time point. This experimental design revealed differences in the physiological sensitivity of individuals with PTSD. However, the temporality of this difference is not known; it is not clear whether the state of PTSD caused sensitivity, or whether this represented a pre-existing trait vulnerability to the disorder. Meta-analyses addressing risk factors for PTSD do not include any studies of physiological sensitivity, but demonstrate that factors such as previous psychiatric history, reported childhood abuse, and family psychiatric history are uniform predictors of PTSD, whereas individual factors such as education, prior trauma and childhood adversity vary in predictive utility according to the population studied and methodology employed (Brewin, Andrews & Valentine, 2000). In addition to the limited research on physiological risk factors, Brewin et al. note that few studies of PTSD risk factors incorporate prospective study designs to evaluate pre-trauma factors leading to increased risk. This is perhaps due to the greater difficulty in planning and conducting such studies as trauma is, by nature, unpredictable. However, a recent study by Wild et al. (2016) evaluated potentially modifiable risk factors in a 'high risk' population of newly recruited paramedics (N = 386). They found 8.3% developed PTSD over a 2 year follow up period and identified pre-trauma predictors of cognitive style, coping style and psychological traits. In another multiple time point study, Bryant, Harvey, Guthrie, and Moulds (2003) investigated the role

of post-trauma physiological arousal in the development of acute stress disorder and PTSD. They found that those with PTSD 2-years-post-trauma had higher heart rate at hospital discharge following a motor vehicle accident. Wang et al. (2017) have explored electrophysiological correlates of PTSD post-trauma and their potential to represent a prodromal state (an early state prior to the onset of a full blown disease or disorder), prior to delayed onset PTSD. Although the study had a very small sample size (N = 65 and n = 5 who developed PTSD) initial results using ROC curves suggested a large effect size for the predictive utility of event-related potentials (AUC of .08; Rice & Harris, 2005). The authors acknowledge that their results may be a "fortuitous consequence of a small sample size" (p. 1) and that it would be useful to combine electrophysiological measures with others biomarkers. No prospective studies have explored the pre-trauma characteristic of psychophysiological sensitivity, but a design that followed a high-risk population could explore this.

As well as variations in experimental design, studies of risk factors for PTSD vary by theoretical orientation, i.e. whether most importance is placed on the cognitive, information processing, behavioural, biological or physiological factors contributing to and maintaining PTSD symptoms. This thesis sought to investigate the effects of PTSD at the psychophysiological level in measuring responses to emotionally arousing stimuli and sensory sensitivity. This orientation was underpinned by research pointing to the role of the hyper-arousal symptom set as most important in the course of PTSD (Schell, Marshall, & Jaycox, 2004; Solomon, Horesh, & Ein-Dor, 2009). From this perspective, hyper-arousal is key to maintaining symptoms by acting as an "engine" which is driving other symptoms (Soloman et al., 2009, p 842). This orientation also forms the theoretical basis for the use of exposure therapy in PTSD; to modify the pathological associations in the fear network and

reduce excessive arousal (McNally, 2007). Although this was the symptom subset used to form hypotheses herein, the current studies cannot underplay the importance of cognitive and behavioural aspects of symptomology, but instead provides a representation of the effect of symptoms at the physiological level. Studies seeking to find biomarkers for PTSD would be advantageous if valid as they unlikely to be vulnerable to malingering in comparison to self-report. These studies do not advocate the use of biomarkers or physiological assessments to replace standard interview or psychometric assessment. However, returning to the concept of convergent validity, future research would profit from a combined biological, cognitive and behavioural approach to measurement, in line with a biopsychosocial approach to studying mental illness. Overall, a study design similar to that of Wild et al. (2016) exploring pre-trauma factors in a high-risk population, such as the emergency services, would be appropriate in exploring whether sensitivity exists as a pre-trauma trait, or is a state induced by the experience of trauma and thus unique to the clinical syndrome.

5.1.3 Categorical and Dimensional Conceptualisations of PTSD

Consistent with the "least drastic" (p. 552) recommendation of Brown and Barlow (2005), this thesis used a categorical cut off score in addition to dimensional exploration of symptom severity and symptom subscales. The results of Experiment Three demonstrated the benefit of dimensional exploration of subscales and was in line with Brown and Barlow's suggestion that "imposing categories on dimensional phenomena leads to a substantial loss of potentially valuable clinical information" (p. 552). However, these findings also demonstrate the limitations of the use of a simple linear PTSD severity score, as particular symptom subscales have differential effects, suppressing the overall effect of a severity scale. PTSD has been considered to be an extremely heterogeneous construct (e.g. Galatzer-Levy &

Bryant, 2013; Leichsenring & Steinert, 2017) so it would be useful for more studies to explore the effect of interventions on subscale scores. A major criticism of current cognitive behavioural and other psychotherapies is that of a lack of a central change mechanism (Kazdin, 2007). Subscale exploration could add validity to the hypothesised mechanism in psychotherapy research, for example, an intervention targeted to reduce intrusive recollections (flashbacks), versus an intervention focussed on increasing positive affect, might have a differential effect on subscales.

Exploration of the effects of subscales in Experiment One demonstrated no dimensional relationships, indicating complexity, in that different dependent variables or outcome measures vary in terms of whether they show a relationship to the categorical PTSD diagnosis, or to individual subscales. Overall, both categorical and dimensional methods appear relevant to the classification and exploration of PTSD and a combined approach is suggested to be useful for research into the symptoms and treatment of PTSD.

5.1.4 Overall Implications

Zoldaz and Diamond (2013) report on the great challenge of developing a behavioural or bio-marker based diagnosis of PTSD. They discuss that PTSD is not the monolithic disorder suggested by the umbrella diagnostic term, but is very heterogeneous, which has complicated research into biomarkers and often been understated in research. This resonates with the findings from the contrast sensitivity study reported herein, but the diagnostic approach was useful in revealing differences in emotional arousal in the pupillometry to images task. This finding has methodological and theoretical implications for the exploration of results in studies of PTSD.

The finding that enhanced emotional reactivity was not specific to threat was unexpected. However, it is possible that a specific effect of threat would be likely if stimuli were ideographic to trauma. In terms of the implications for the clinical presentation of PTSD, the physiological picture from these studies suggests that it is not only the retrieval or re-experiencing of trauma-relevant stimuli that activates higher physiological responses (consistent with studies of resting arousal e.g. Jovanovic, Norrholm, Sakoman, Esterajher, & Kozarić-Kovačić, 2009). Both the reduced PLR and the contrast threshold study suggests that sufferers experience a state of constant over-arousal, combined with this greater reactivity to even non-threatening emotional stimuli. Individuals in this study were not recently traumatised, representing the chronicity of this physiological expression as well as a failure to learn and habituate to non-threatening stimuli.

Behavioural markers have demonstrated their utility in other areas of psychological research. For example, the use of the Implicit Association Test (IAT; Greenwald, McGhee, & Schwartz, 1998) in forensic psychology to assess implicit attitudes toward violence in murderers (Snowden, Gray, Smith, Morris, & MacCulloch, 2004) and attitudes toward children in paedophiles (Gray, Brown, MacCulloch, Smith, & Snowden, 2005). Recently (2016), a National Institute for Health Research clinical trial has been initiated to incorporate a computer software measure of negative attentional bias in depression as an indicator for responsivity to antidepressants. The study is operating across the UK, France, Germany, The Netherlands, and Spain but is incomplete at present. Currently there is no evidence of the uptake or efficacy of this type of paradigm in Primary Care or mental health services outside of psychology. Pupillometry could be compatible with such a study, especially due to the rapid administration time and simple passive viewing task, which was also tolerable in a clinical sample. The predictive utility of any behavioural or physiological measure of

psychiatric disorder is unlikely to ever be perfect, but such measures can be useful in either assisting diagnosis, building convergent validity to support a construct, or, perhaps most usefully, quickly and easily assessing potential changes in performance linked to treatment outcomes without having to repeat lengthy interviews.

5.1.5 Overall Limitations

Despite many studies employing ideographic trauma-stimuli (for example, script driven trauma imagery) the current work employed trauma-nonspecific stimuli in the emotive images and sounds tasks, and measured baseline performance using no stimulus manipulation in assessment of visual contrast threshold. Pole (2007) demonstrates that studies of baseline arousal typically result in smaller effect sizes, consistent with the results of Experiment Three. Many of the images used in Experiment One were associated with violence, and most traumas in the sample involved sexual violence, suggesting that the stimuli were not entirely trauma-nonspecific, as they did depict some violence. However, the observed reactivity was also apparent for happy images which are necessarily trauma non-specific. No other studies of pupil response in PTSD have employed emotion control conditions such as the happy and sad images, but it would be useful to include these in future studies. It is possible that using ideographic trauma imagery would lead to greater effect sizes, and provide more evidence for threat-specific hyper-arousal. However, given the difficulty in matching stimuli across categories and stimulus properties, in addition to the potential ethical issues and sampling difficulties this would produce, the current study supports the use of a stimulus set in future work which is not trauma specific.

There are many complicating factors in defining and assessing PTSD. This study did not isolate a specific trauma sample, for example, veterans, sexual assault survivors, or

victims of interpersonal violence. Although, nine of the twenty-three individuals reported sexual violence as an index event, the rest of the sample was extremely diverse. This diversity may have affected the variation in responses to specific stimuli. Another factor which may specifically affect the physiological expression of PTSD is the experience of discrete versus recurrent traumatic events. The current study sample had seldom been treated for psychological trauma, reported psychiatric histories, reported significant symptom duration, and multiple adverse life events and potential traumas. The psychiatric inpatient sample recruited for task development suggested that this kind of demographic is likely to reflect a reality in clinical in-patient settings (see Appendix C). Much research views previous PTSD as a sensitising event for the risk of future PTSD (Breslau & Peterson, 2010) but the 'type of trauma' demographic is difficult to measure. Herman (1995) first defined complex trauma as prolonged exposure to coercive control, such as occurs in concentration camps, cults, and severe cases of child abuse. Overlap between Borderline Personality Disorder (BPD) and complex trauma is also suggested within the literature. For example, individuals with a diagnosis of BPD are hypothesised to have a high biological vulnerability to emotion dysregulation, including high arousal to emotionally evocative stimuli (Linehan, 1993). However, some physiological experimental data do not support more intense emotional reactions during passive viewing, or emotionally modulated startle (Herpertz, Kunert, Schwenger, & Sass, 1999). Experimental evidence reported by Kuo and Linehan (2009) suggested that BPD individuals' extremely intense negative emotional reactions can be accounted for by a highly aroused starting point, rather than high reactivity during task performance. Within a PTSD sample, McTeague et al. (2010) report a striking moderation effect by cumulative versus discrete trauma on physiological reactivity. The authors used a startle paradigm in which individuals imagined threatening and neutral scenarios while the

eye-blink response was recorded. Individuals who had been exposed to multiple traumas demonstrated blunted defensive reactivity, despite higher reported arousal, whereas the single trauma group showed a robust, heighted reactivity to startle probes. These studies stress the importance of measuring and defining chronic and severe, multiple trauma PTSD for both research purposes and clinical practice and comprehensively describing the clinical sample recruited to consider confounds.

Finally, although every effort was taken to ensure subjects would not be motivated to lie about medication or illicit substance use, these studies was dependent on self-reported use, rather than established drug testing. Future studies seeking to replicate or build upon the results here may want to include a drugs test, although this would invite extra cost and effort. The results here did not exclude participants based on psychotropic medication use, but sought to recruit a sample in which there was lower use than in psychiatric inpatients, to clearly describe reported use, and explore potential effects. No supplementary analyses revealed any potential effect of medication within this sample, but preparatory work revealed detrimental effects of medications on visual contrast thresholds. Future work employing visual methods should exclude individuals using opiates, and consider the literature and theoretical basis for alterations in performance that have been demonstrated in individuals using psychiatric medication to either obscure an expected result, or artificially enhance it.

5.1.6 Conclusion

The studies reported herein used novel methods to demonstrate heightened physiological arousal to emotive stimuli in individuals with PTSD. There was evidence for greater physiological arousal across different categories of emotive images, demonstrating promise for the use of pupillometry in the assessment of PTSD. A multi-dimensional analysis

afforded investigation of more complex relationships between visual contrast threshold and PTSD subscales. The effect of the multidimensional analysis has theoretical implications for research assessing PTSD as a homogenous construct, and supports the dimensional exploration of PTSD subscales.

Overall, these exploratory studies provide evidence for physiological sensitivity in fully expressed PTSD, but the potential for sensitivity to predict PTSD is yet to be explored. The thesis provides a basis of evidence as well as recommendations for future research that could explore pre-trauma physiological risk factors in the measurement of sensitivity to the development of PTSD.

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Appendices

Appendix A Psychiatric Medication and Basic Vision

1.1 Introduction

Use of prescription psychotropic medication is common in clinical samples targeted for participation in psychological and psychiatric research. Psychotropic medications are any prescription drugs with the potential to alter the mind, emotions, or behaviour and broadly include anti-psychotic, antidepressant, anti-obsessional, anti-anxiety, anti-panic, stimulant and mood-stabilising agents. Investigation of the cognitive effects of psychotropic agents is complex, as the presence of cognitive impairment (departures from average in IQ, memory, processing speed etc.) is often a function of the mental illness itself (e.g., Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). It is necessary to be able to dissociate the effects of the symptoms of illness versus the effects of medication on cognitive function. If not accounted for, these mind-altering drugs have the potential to severely confound psychological research, and require careful consideration of exclusion criteria and control in order that conclusions drawn from research employing these samples can be considered as valid. This review will focus on the research literature highlighting the effects of psychotropic medication in visual perception, with the eye being shown to be the second most frequent organ to manifest drug toxicity, after the liver (Li, Tripathi, & Tripathi, 2008). The review will focus on contrast sensitivity and pupil dilation in terms of basic vision, and attentional processes for visual cognition. Consideration will also be given as to whether the effects of each medication are non-specific, for example sedative and affecting global processing, or causing a specific dissociable impairment. The research reviewed has largely been conducted and documented in two ways; the first, more common method involves an acute dose of medication to a healthy participant and the second involves the assessment of

chronic psychotropic users, usually in clinical samples. The relative effect of the disorder versus the medication can be partially disentangled if research is conducted in this way.

1.2 Anxiolytics: benzodiazepines

Benzodiazepines are a class of psychoactive drugs with tranquilising properties. They act as a depressant to the central nervous system (CNS) by affecting the transmission of gama-Aminobutyric acid (GABA), the chief inhibitory neurotransmitter in the brain, to produce a sedative anxiolytic effect. There is robust evidence to suggest that GABA acts as an inhibitory transmitter within the visual cortex (Iversen, Mitchell, & Srinivasan, 1971) and, as benzodiazepines serve to potentiate the actions of GABA, this is a proposed mechanism through which this class of drugs have an ocular effect. Benzodiazepines are widely prescribed for anxiolytic, hypnotic, antiepileptic, and muscle relaxant properties and are often used to reduce agitation in hospitalised patients on a pro re nata (PRN or 'in the circumstance') basis. The research literature on benzodiazepines involves the study of single dose, acute administration to healthy volunteers (a neuropsychological approach) versus recruitment of long-term users. Efforts have also been made to assess whether the effects of this medication are non-specific, and globally disruptive to cognition, or impact on a particular visual pathway.

An early study assessing the effects of benzodiazepines on visual cognition and basic vision was conducted by Preston et al. (1988). This study looked at the effects of the drug lorazepam at 0.5mg, 1mg, or 2mg doses versus placebo. Fifteen healthy subjects participated over weekly intervals. Lorazepam produced a dose-related increase in self-reported sedation, and deficits in verbal secondary memory, simple choice reaction time, stroop, and vigilance. The results from these attentional tasks suggest a non-specific global decrease in attention

and visual cognition, with reaction times being particularly impaired. Interestingly, the authors also found a specific and selective enhancement of contrast sensitivity after administration of 1mg of lorazepam only, and impairment at 0.5mg and 2mg doses, resulting in a cubic trend, or an inverted U-shaped facilitation effect. The contrast sensitivity methodology involved the use of static gratings of 4 cycles per degree to assess acuity at high contrast, and sensitivity at low contrast. The findings consistently showed no impairment in acuity. The authors suggest this result might be explained by the effect of inhibitory GABA selectively enhancing visual functions reliant on lateral inhibition, however, no further research appears to have replicated this facilitating effect. Following this research Blin, Mestre, Paut, Vercher, and Audebert (1993) conducted a study on visual contrast sensitivity and midazolam. Here the authors administered midazolam, a drug prescribed for rapid sedative properties to agitated patients, in a repeated measures design to healthy participants. The authors measured contrast sensitivity to temporally modulated gratings of 0.25, 1 and 4 cycles per degree, and assessed performance over 5 time intervals, up to 4 hours post administration. The study found a global reduction in visual sensitivity, but, more specifically, this loss of sensitivity was limited to the grating stimuli of medium to high spatial frequencies. The authors suggest a possible explanation for this could be a change in size of the receptive fields, or a selective impairment of the parvocellular visual channels. However, a study conducted by Harris and Phillipson (1995) indicated that the loss of sensitivity occurred at lower spatial frequencies, particularly 0.2 cycles/degree, although the statistical analysis across spatial frequencies proved non-significant. This study also employed a monocular viewing paradigm, in contrast to the rest of the literature reviewed, which employed binocular viewing. Binocular viewing has been shown to robustly increase

contrast sensitivity (Derefeldt, Lennerstrand, & Lundh, 1979), perhaps making this lorazepam induced impairment appear more pronounced.

Research into ocular effects of chronic benzodiazepine use is limited. Giersch, Speeg-Schatz, Tondre and Gottenkiene (2006) conducted a study to assess static contrast sensitivity in long-term users of lorazepam. Consistent with previous results, they found visual acuity to be preserved, but contrast sensitivity to be generally impaired in the same manner as was resultant from an acute dose. The results also suggest this impairment to be limited to medium to high spatial frequencies, with the most intact performance occurring at 0.5 cycles/degree. The authors conclude that lorazepam administration effects visual contrast sensitivity by raising thresholds in a way which is dissociable from other benzodiazepines.

That benzodiazepines influence basic vision appears to be a robust finding, although there is perhaps more evidence to suggest this impairment exists within the parvocellular stream of the visual system, and is more strongly linked to lorazepam in terms of visual contrast sensitivity. It has been consistently shown that these medications do not impact on visual acuity, and thus require a wider range of perceptual assessment to discern effects (Richa & Yazbek, 2010). The benzodiazepine class has been shown to robustly impair episodic memory (Pompéia, Manzano, Tufik, & Bueno, 2005) i.e. memory of recent events, of the circumstances surrounding them and of the order in which they occurred, and explicit memory inclusive of recall and recognition (Kothary, Brown, Pandit, Samra, & Pandit, 1981). There also appears to be dissociable effects of lorazepam on visual attention. Studies have shown that lorazepam impairs many aspects of cognition including the velocity of saccadic eye movement (Buffett-Jerrott & Stewart, 2002), perceptual priming (a form of implicit memory) (Brown, Brown, & Bowes, 1989), perceptual integration (filling in the gaps in

shapes) (Beckers, Wagemans, Boucart, & Giersch, 2001) and an ERP study suggests that lorazepam induces atypical central visual processing changes, over and above that of a comparative benzodiazepine, and that these effects are more pronounced in the visual, rather than the auditory modality. Moreover, research by Boucart et al. (Boucart, Visme, & Wagemans, 2000; Boucart, Waucquier, Michael, & Libersa, 2007) has shown that diazepam impairs the temporal dynamics of attention. The authors used an 'attentional blink' paradigm, in which participants were asked to view a rapid serial presentation of images and identify a target city name, followed by identification of a vehicle 'probe'. The probe appeared at variable time intervals after the target, on the left or right hand of the screen. In a 'single task' control condition, participants were asked to ignore the city name. The authors found that both the magnitude of the attentional blink, and the duration was increased in the diazepam condition in a dose response manner, with those receiving a higher dose showing a greater attentional deficit. Participants receiving this higher dose required more than 600 milliseconds to be able to perform the dual task, suggesting that diazepam at this therapeutic dose impairs attentional shifting when participants had to identify two targets occurring in rapid succession.

1.3 Antidepressant medication

Tricyclic antidepressants (TCAs) and Selective Serotonin Reuptake Inhibitors (SSRIs) are the most commonly used antidepressants in the treatment of mental health problems (Wadsworth, Moss, Simpson, & Smith, 2005). It has been found that TCAs cause transient blurred vision in up to one-third of patients. However, there is no evidence investigating the role of antidepressant medication in contrast sensitivity and basic vision, save for one study by Bubl, Kern, Ebert, Bach, and van Elst (2010). The authors recruited forty individuals with

major depressive disorder of whom half were taking medication and half were unmedicated. The measure involved the use of an electroretinogram (ERG) to assess contrast gain in the retina. The ERG is a diagnostic test that measures the electrical activity generated by neural and non-neural cells in the retina in response to a light stimulus, in this case, a chequerboard of varying contrasts. The study suggested that, regardless of medication, depressed patients had dramatically lower retinal contrast gain. There was also a strong correlation between this deficit and the severity of the reported symptoms. What's more, receiver operator characteristic analysis demonstrated excellent specificity and good sensitivity, correctly classifying 31 of the 40 depressed patients. In terms of medication, there was no significant difference between the medicated and non-medicated groups. However, the authors note that the individuals taking medication had not been in receipt of this treatment for long enough periods of time in which to assess whether the medication had an effect in this instance. This study highlights a potential for a psychiatric disorder to produce significant effects on the visual system, but the effects of antidepressant medication are not known.

1.4 Antipsychotic medication

There is anecdotal evidence of rare cases involving hyper-vision after taking anti-psychotic medication. Uchida, Suzuki, Watanabe, and Kashima published a case study (see, Uchida et al., 2006) of an individual whom had self-reported enhanced vision; however, no assessments of visual function or contrast sensitivity were conducted to quantify these effects. The authors note that, in the past, this hyper-vision had been attributed to schizophrenia spectrum disorders, and highlighted the case study as being unique in that the individual did not suffer any such disorder. More recent research has identified a role for enhanced sensory perception in unmedicated, first episode schizophrenia, again implicating a

role for a disorder in altered visual perception, rather than an effect of medication (Kiss, Fábián, Benedek, & Kéri, 2010). Kiss et al. investigated the role of anomalous perceptual experiences with the Structured Interview for Assessing Perceptual Anomalies (SIAPA). The authors administered two assessments alongside this interview, the first to assess parvocellular contrast sensitivity, and the second to assess magnocellular contrast sensitivity. The enhanced performance of the clinical group versus the control subjects was particularly apparent at the two lowest spatial frequencies (between 0.25 and 0.5 cycles per degree). As a complement to this finding, studies reporting impaired contrast perception in schizophrenia spectrum disorders have been rebuked by Chen et al. (2003). The authors suggest that as the mechanism for contrast detection in the visual system is, in part, mediated by dopamine then dopamine blocking antipsychotic medication may be responsible for these reports of impairment. There are two classes of antipsychotic medication. Typical antipsychotics represent the older class of drugs and include commonly used medications such as depot neuroleptics, whereas atypical 'newer' medications include clozapine and quetiapine. In terms of D2 dopamine receptor sites, atypical antipsychotics maintain loose occupancy for a shorter period, whereas the typical variety maintain essentially undiminished occupancy for days, lowering the amount of dopamine available to the visual system. Chen et al. (2003) found that patients with a diagnosis of schizophrenia spectrum disorder in receipt of typical antipsychotic medications had significantly elevated contrast thresholds, and were impaired in comparison to those receiving atypical, both, no medication, and a control population without a diagnosis of schizophrenia. This study highlights the problems in drawing conclusions from participants in receipt of psychotropic medication. Most studies (e.g. Butler et al., 2005) have drawn conclusions that visual contrast sensitivity is impaired, particularly within the magnocellular pathway, in schizophrenia spectrum disorders. However, the

authors state that "*All patients were receiving antipsychotic medications at the time of testing*" (p.497). Although, they also failed to replicate the results of Chen et al. (2003) in that they found deficits within users of atypical antipsychotics also.

1.5 Analgesics: opiate forms

Although analgesic medication does not fall under the class of psychotropic, research suggests a co-morbidity between chronic pain and psychiatric illness (Gatchel, 2004), and a number in the psychiatric sample used for the pilot study were in receipt of opiate analgesics. The research on opiates and visual contrast sensitivity is, again, very limited. There is one early study looking at visual contrast discrimination in conditioned pigeons (Blough & Blough, 1989). This study found that, at higher doses and higher spatial frequencies, pigeons were impaired in their contrast detection. However, this finding doesn't appear based in any specific visual pathway. It is likely that, as opiates also act as sedatives, they serve to impair performance in a global fashion like lorazepam (Preston et al., 1988).

1.6 Psychotropic Medication and Pupillary Function

This final section will pay consideration to the effects of psychotropic medication on pupillary function. Studies of pupil dilation are becoming increasingly popular as a proxy for studying the impact of emotion in the autonomic nervous system. The diameter of the pupil represents an equilibrium between the physiologically antagonistic sympathetic (pupil dilatation or mydriasis) and parasympathetic (pupil constriction or miosis) influence on the iris (Bitsios, Philpott, Langley, Bradshaw, & Szabadi, 1999). Sympathetic innervation to the eye acts to contract the radial muscles in the periphery of the iris called the dilator pupillae. Parasympathetic innervation acts on the muscles of the sphincter pupillae, the fibres of which

contract causing constriction of the pupil. The pupillary light reflex (PLR) amplitude is almost exclusively determined by parasympathetic activity, with parasympathomimetic drugs increasing and parasympatholytic drugs decreasing light reflex response amplitude (Loewenfeld & Lowenstein, 1993). The term 'reflex' is slightly misleading here, as cognitive and other factors acting on the parasympathetic nervous system can influence the response, in addition to optical reflexive factors such as ambient luminance levels. It is therefore evident that psychotropic and other medications known to alter either of these two systems will have an impact on both pupil dilation, and the PLR, which in turn has implications for using these methods as an indirect or outcome measure in clinical samples in which usage of these drugs are prevalent.

The benzodiazepine class acts as a depressant to the central nervous system, causing a decrease in arousal and a potent sedative effect. It is generally accepted that there is a close relationship between sedation, or low arousal, and pupillary function (Loewenfeld & Lowenstein, 1993); a decrease in arousal is associated with a decrease in pupil size (Hou, Langley, Szabadi, & Bradshaw, 2007). Hou et al. investigated the effect of the benzodiazepine diazepam on pupillary function. The authors compared diazepam to a first-generation antihistamine, diphenhydramine, on the basis that these two drugs are sedative, but atypically so. They are considered atypical as although they induce a sedative effect they also directly influence, by a separate pharmacological action, the pupil control mechanism. The generally assumed relationship between sedation and pupil size is therefore confounded by this direct relationship. The authors compared the effects of single doses of these two medications on indices of pupillary function (diameter, light reflex) and levels of arousal in healthy volunteers. Non-pupillary autonomic indicators of arousal were also measured by cardiovascular function (heart rate) and sweat gland activity assessed by measuring skin

conductance. Consistent with early reports (Sigg, Keim, & Kepner, 1971) the study found no effect of diazepam on pupillary function (dilation or light reflex), whereas diphenhydramine induced significant miosis (constriction) at all luminance levels. That neither drug influenced the light reflex is also unique in that, as mentioned above, amplitude of the light reflex response is almost exclusively determined by parasympathetic activity. In terms of applications to clinical work, the pupillary light reflex has been applied to models of human anxiety. More specifically Bitsios, Szabadi, and Bradshaw (1996) have modelled the 'fear inhibited light reflex' in response to psychological threat of electric shock. The authors showed that under conditions of threat there was a consistent increase in initial pupil diameter, a decrease in light reflex amplitude and a concomitant increase in alertness and anxiety ratings. Later work from Bitsios et al. demonstrated the impact of psychotropic medication on this reflex. Bitsios et al. (1998b) demonstrated that clonidine, a sympatholytic drug used to treat a range of disorders including ADHD, anxiety, withdrawal and high blood pressure, had a non-specific action on pupillary function. Administration of this medication reduced pupil dilation and light reflex in both 'safe' and 'threat' conditions, as opposed to acting only in conditions of threat as an anxiolytic would. Conversely Bitsios et al. (Bitsios, Szabadi, & Bradshaw, 1998a) showed that administration of diazepam had a specific, rather than global, reduction effect on the pupillary light reflex under conditions of threat. This reduction was not apparent in either a change in pupil size, nor in the 'safe' condition, and is contrary to the findings of Sigg et al. (1971) and Hou et al. (2007). The critical difference between these two studies is in the pupillometry methodology; with the study of Bitsios et al. (1998a) assessing the PLR in response to psychological threat, rather than a neutral, optical factor such as luminance. This enhances the point that, when studying psychiatric samples, it is important that the population is not being pharmacologically 'treated' for the disorder that

you are looking to assess, and that basic pharmacology studies or generalisations about classes of medications cannot reveal the whole picture with regards to these medications.

In terms of other psychotropic medications, reports indicate a risk of glaucoma in some individuals taking antidepressants, inclusive of both TCAs and SSRIs (Costagliola et al., 2008; Lieberman & Stoudemire, 1987). Research suggests that serotonin (5-HT) has an impact at the level of the iris, and that particular 5-HT receptor types are involved in relaxation of the sphincter of the pupil (Costagliola et al., 2008). This would suggest dilation after taking SSRI medication, which has been confirmed in studies of sertraline administration and pupil size (Saletu & Grünberger, 1988; Schmitt, Riedel, et al., 2002). Individuals being treated for depression also show reduced PLR compared to controls, which persists during treatment with SSRIs and after, when the individual is considered 'recovered' (Bär et al., 2004). Bär and colleagues suggest that medical treatment had a larger effect on autonomic function, as measured by the pupil light reflex (PLR), than the state of depression itself. Theofilopoulos, McDade, Szabadi and Bradshaw (1995) reported the effect of non-SSRI antidepressants on pupil kinetics, and suggest that the amplitude of the PLR is consistently reduced under antidepressant versus placebo at all levels of light intensity. This reduction was in the range of 0.5 mm (after dark adaption). It is not clear whether this effect would still be apparent in a lit room as no studies have addressed this.

As SSRIs are commonly prescribed, there are also studies assessing their impact on vigilance (in this context, vigilance refers to reaction time and alertness). Again, the effects are complex, with doses of sertraline (20 – 40 mg) producing no effect, reportedly due to the co-action of dopamine reuptake inhibition, whereas paroxetine impairs vigilance at all doses (Schmitt, Ramaekers, et al., 2002). Studies assessing higher doses of sertraline show the

moderating effect of dosage on findings. Saletu and Grünberger (1988) suggest vigilance enhancement assessing psychophysiological variable (EEG and pupil dilation) at 100 mg doses, but vigilance impairment at 200 mg doses (along with more side effects, such as nausea and vomitting). Again, these studies demonstrate that effects are not consistent within drug classes and are also moderated by dose. It is not clear whether chronic use of SSRI such as sertraline at high doses would still produce effects, or whether a tolerance would build.

The great majority of visual opiate research pertains to toxicity, overdose, and uncommon side effects reflected in case report methodology. Case studies suggest that overdose and toxic doses of both antipsychotics and tricyclic antidepressants can lead to dilated pupils (Derenne & Baldessarini, 2005; Spiker, Weiss, Chang, Ruwitch, & Biggs, 1975). In contrast, singular ('safe') doses of opiates including heroin, morphine, codeine, oxycodone, oxymorphone and hydrocodone significantly constrict pupils, reduce the pupillary light reflex, and reduce the speed of the return to baseline from constriction (Pickworth, Welch, Henningfield, & Cone, 1989). Narcotics act to produce miosis or 'pinpoint' pupils, which would be less mobile, and there is a vast literature on this effect. The literature on opiates also demonstrates that the effects of medication are complex, depending on metabolism, dose, and frequency and severity of use. For example, even the often cited pinpoint pupils seen in heroin users can vary according to whether narcotic agonists are regularly taken, or taken in single dose (Elliott & Way, 1961) and whether an individual has just taken the drug (miosis), or is experiencing withdraw symptoms or has overdosed (mydriasis) (Robinson, Howe, Varni, Ream, & Hegge, 1974). Research also suggests that pupil responses vary according to acute, but not long term drug use (Tress & El-Sobky, 1979) indicating a build-up of 'tolerance' for medication. More commonly used opiate painkillers include tramadol and codeine. Tramadol has been shown to affect measures of static

pupillometry, leading to a dose-dependent decrease in initial pupil diameter, in comparison to placebo (Matouskova, Slanar, Chytil, & Perlik, 2011). Importantly, this study also showed a difference in metabolism rates, with only the extensive metabolisers (EM participants) showing this pupillometry effect, and not the poor metabolisers (PM participants), highlighting another mediating complexity in this field of research. A study on monkeys has also shown miosis to occur following administration of chlorpromazine (Kumar, Palit, & Dhawan, 2003)

1.7 Conclusion

To conclude, this review has addressed the effects of psychotropic medications on contrast sensitivity, a dimension of basic vision, and pupillary function. The information has been reviewed with the aim of assessing the impact of psychotropic substances as a confound in psychological research employing visual methodology. Examples of potentially erroneous conclusions drawn from medicated populations have been illustrated from review of the literature on visual contrast impairments and schizophrenia. Evidence suggests that each medication manifests significantly within the visual system, including very specific impairment such as high spatial frequency contrast discrimination in benzodiazepines (Blin et al., 1993) to global performance decrements due to sedative effects in not only the visual system, but global central nervous system. These effects are massively complex and similar results do not seem to be produced by medications within the same class (e.g., 'antipsychotic' or 'SSRI' classes) and, furthermore, effect is moderated by dose, along with individual factors such as metabolism, body mass and tolerance/ withdrawal state. It is suggested that studies attempt to reduce the recruitment of individuals taking acute doses of multiple medications (or intermittently using illicit substances). Where this is not possible, in studies

of severely impairing psychiatric disorder, careful consideration of the types of medication in use is necessary. For example, checking that results are not a product of a known-effect of a medication. Users of opiate based substances should be excluded entirely from pupillary studies. These drugs have the largest effect on the pupil, effects which are noticeable to the human eye, and can influence ceiling or floor effects to measurement of pupil size. The effects of opiates are also dependent on whether an individual is in a withdrawal state or has recently used.

1.8 Supplementary Medication Analyses

1.8.1 Descriptive Analysis of Medication Use within the Current Sample

The current sample were using much less medication than the secure psychiatric hospital sample (see Appendix C, Table C25). Within the whole sample of 80, 31 individuals were taking psychotropic medications, of the sample of 65 individuals included in experimental chapters, 24 were taking medication. The frequency of type of psychotropic medication use is outlined in Table A20. Four individuals taking prescribed opiates (e.g. subutex, methadone, oramorph and tramadol) were excluded entirely. The range of combinations after exclusions was 1 – 3. One individual was taking 3 types of medication, and four individuals were taking 2 types. The combinations of medications in use within this sample were less complex than in the hospital sample. Individuals taking opiate medications (illicit and prescribed) were also using combinations of 4, 5 and 6 other psychotropics, suggesting high levels of pathology and potential for psychotropic interference. The most commonly used medication was antidepressants.

Table A20. *Psychotropic Medication Use in Individuals Included in Experimental Chapters (N = 65)*

Medication type	Frequency
Anti-anxiety	3
Anti-depressant	
SSRI	11
Other (tricyclic and NSRI)	10
Anti-psychotic	2
Mood stabilising	0

1.8.2 Supplementary Analysis for Chapter 3, Experiment 1: Effect of Antidepressants on the Initial Constriction Response

A median split of PTSD severity scores indicates an individual within a 'high-trauma' group has a CAPS-V score of 18 or over. The twenty-six individuals in the high-trauma group (exclusion criteria based on Experiment One) were divided into two groups of individuals; 14 of whom were taking no antidepressants and 12 of whom were taking prescribed antidepressants. PTSD symptom severity did not differ significantly between the no-antidepressant group (M = 35.93, SD = 15.01) and the antidepressant group (M = 42.00, SD = 14.18) ($t(24) = -1.05$, $p = .30$), suggesting the groups had coincidentally comparable levels of symptoms. A comparison group of 19 individuals who were not taking antidepressants and had experienced a traumatic event, but reported no symptoms (CAPS-V score of 0), were used to assess any differences in the amplitude of the ICR to neutral images (chosen as it was significantly related to PTSD symptom severity and devoid of emotional content influencing amplitude). A one-way ANOVA with groups of 1) high-trauma, no antidepressant, 2) high-trauma, antidepressant and 3) no-trauma, no antidepressant was conducted on the mean constriction amplitude to neutral images 500 – 1000 ms post stimulus onset. There was a significant main effect of group $F(2, 42 = 8.98$, $p = <.001$, $\eta_{p2} = .30$. Planned comparisons revealed no significant difference between the high trauma groups ($p = .56$) but there were significant differences between both high trauma groups and the no trauma groups ($ps <.003$, see Figure A22).

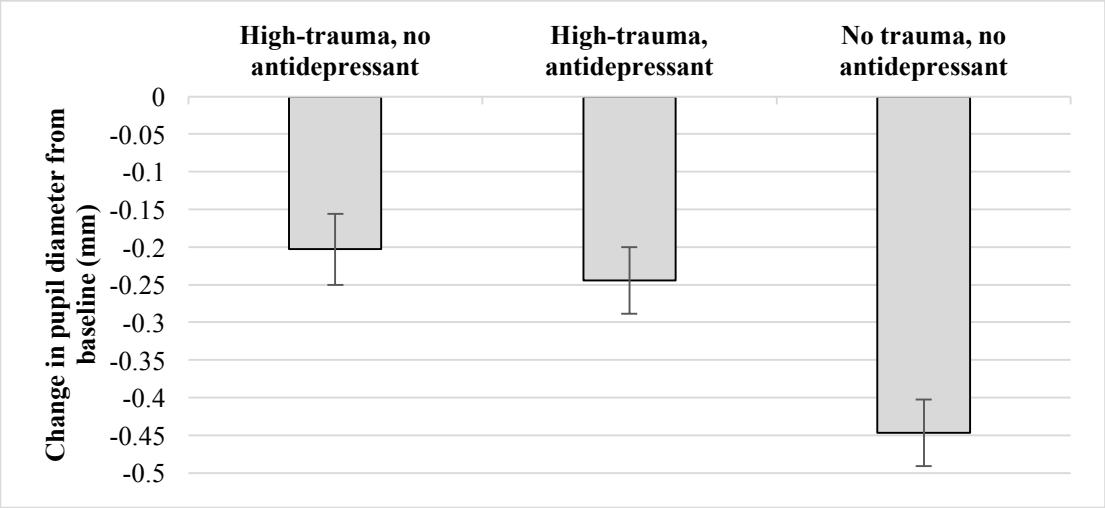

Figure A22. Comparison of ICR to neutral images for individuals prescribed antidepressants versus those who were not. Error bars represent +/- 1 standard error.

1.8.3 Supplementary Analysis for Chapter 3, Experiment 1: Effect of Any Psychotropic Medication on Emotional Modulation

There is no literature to suggest an enhancement of emotional reactivity due to psychotropic medication, on the contrary, these medications usually have a sedative effect or aim to reduce strong emotional reactions. There is also no way to know within medication analyses whether the individuals who were prescribed a medication of some form were 'different' in some way which would confound a comparative analysis. However, an analysis splitting the PTSD positive group into individuals taking any psychotropic medication (n = 10) compared to those not taking any psychotropic medication (n = 10) was conducted, comparing the emotional modulation scores between the two groups. There was no significant difference in symptom severity between the groups (p = .927) and multiple t-tests suggested no significant difference in emotional modulation to fear, happy or sad images within the 1000 – 2000 ms analysis window (all ps ≥ .264).

1.8.4 Supplementary Analysis for Chapter 4, Experiment 3: Effect of Psychotropic Medication on Visual Contrast Threshold

There were no categorical differences in visual contrast thresholds suggesting individuals with a diagnosis of PTSD performed better than those who did not meet diagnostic criteria. However, twenty-three individuals included in this analysis reported taking a form of psychotropic medication versus forty-four who did not (see Table A20 for details of types of medication). A comparison of the mean contrast threshold between individuals taking medication (M = .0125, SD = .0025), versus those who were not (M = .0118, SD = .0039) suggested no significant differences between these groups $t(65) = -0.76$ p = .451).

Appendix B Supplementary and Exploratory Analyses

2.1 Experiment One

2.1.1 Group Differences in IPD

An exploratory analysis of IPD in individuals with a CAPS-V symptom severity score of more than 40 was conducted, as a comparison to the proposed study methods listed in a pre-registered clinical trial ('A Pilot Dose-Response Biomarker Study of Brexpiprazole Treatment in PTSD', 2017). The group (N = 48) was divided into those with CAPS-V scores which were over 40 (n = 10) and those with scores under 40 (n = 38). The differences in group size are not ideal, but an exploratory analysis showed no significant difference in IPD between the lower symptom severity group (M = 4.01, SD = 0.97) and the higher severity group (M = 3.87, SD = 0.60) (t(48) = -0.42, p = .67).

2.1.2 Categorical Differences in Emotional Modulation to Emotive Images using the Impact of Event Scale-Revised

An IES-R score of more than 37 has been associated with reductions in immunity (Kawamura, Kim, & Asukai, 2001), and is slightly higher than the 33/88 recommended clinical cut-off for a probable PTSD diagnosis (Creamer, Bell, & Failla, 2003). As a screening tool, the sensitivity of the IES-R is likely to be higher, but the specificity lower so a more conservative cut-off was chosen for this exploratory analysis. For Chapter 2, Experiment One the division of the group of individuals who had experienced a Criterion A traumatic event indicated 22 individuals to score over 37 on the IES-R and 26 to score under 37. Of the 22 'high IES-R' individuals, 5 were classified as not meeting the diagnostic

criteria for PTSD using the CAPS-V and 3 individuals in the 'low' IES-R group did meet diagnostic criteria. An analysis of the significant pairwise comparisons of the emotional modulation scores 1000 – 2000 ms period post stimulus onset and the ICR 500 -1000 ms post stimulus onset are illustrated below for this grouping (Figure B23). The pattern of higher emotional modulation for individuals with high IES-R symptom severity scores is retained.

The multivariate analysis of covariance (MANCOVA) showed no significant effect of the covariate, age (p = .525) or a main effect of group on emotional modulation scores (p = .318). Univariate tests assessing the effect of group on emotional modulation suggested a significant effect of fear images (p =.054, η2 = .08) and pairwise comparisons suggested that the high IES-R group (M = 0.10, SD = 0.10) showed greater emotional modulation than the low IES-R group (M = 0.04, SD = 0.11) (p = .014, d = 0.60). Univariate tests for sad and happy stimulus types were non-significant (ps > .125).

The effect of the IES-R grouping on the ICR was marginally significant with a medium effect size (p = .075, d = 0.54). A comparison of the means using the CAPS-V PTSD positive and PTSD negative groups showed this to be significant with a large effect size (p = .019, d = 0.71).

Overall, the results using the IES-R support the trends found within the main analysis of Experiment One.

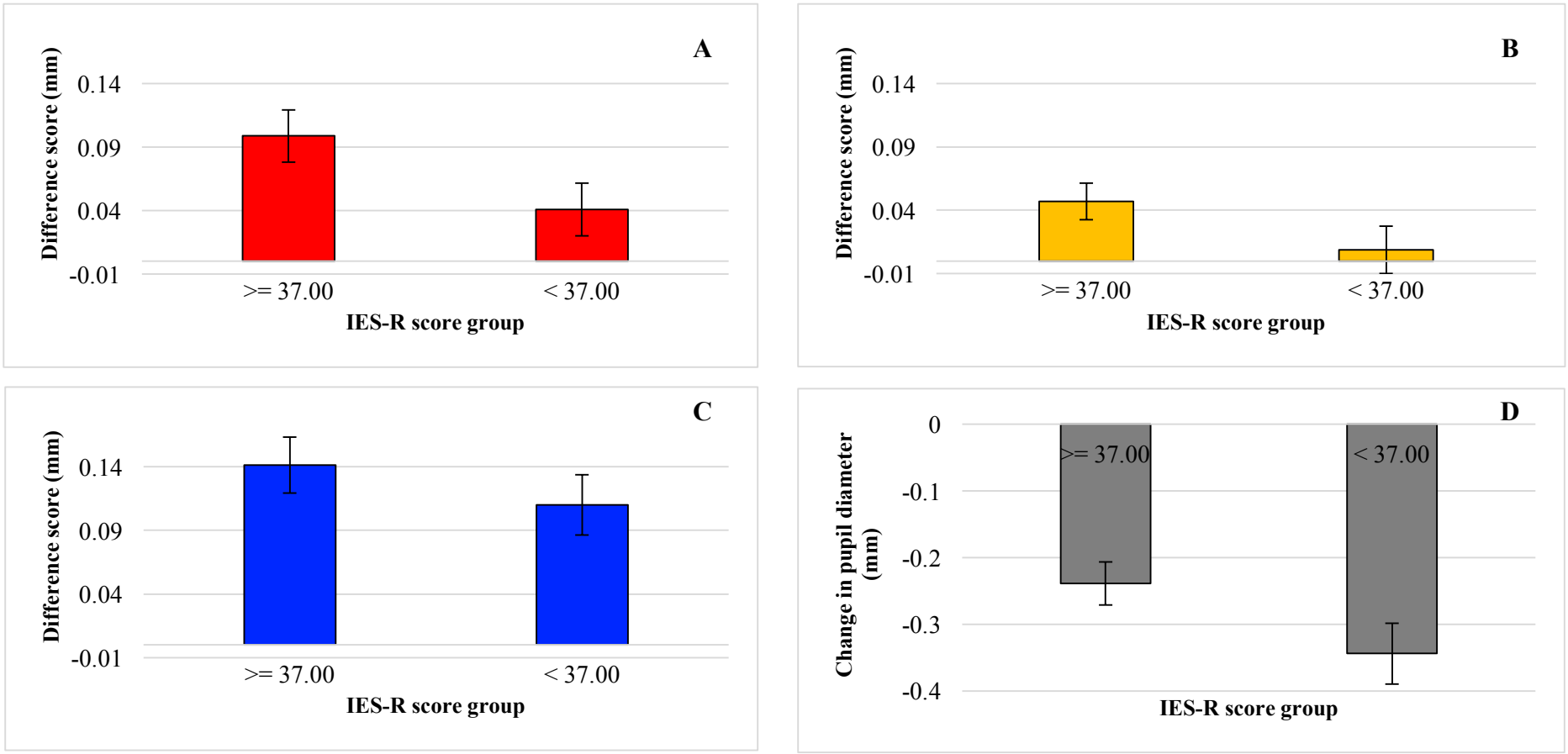

Figure B23. Groups of high (n = 22) and low (n = 26) IES-R scores and pupillary outcome measures from Experiment One. A = emotional modulation by fear images. B = emotional modulation by happy images. C = emotional modulation by sad images. D = initial constriction response for neutral images.

Table B21. *Regression Statistics Examining Relationships Between IES-R PTSD Symptom Scales and Indices of Pupil Function in the Trauma Sample (n = 65)*

	Intrusion				Avoidance				Hyper Arousal				
Criterion Variable	*r*	β	*t*	Unique sr^2	*r*	β	*t*	Unique sr^2	*r*	β	*t*	Unique sr^2	R^2 *p*
IPD	.06	-.29	-1.10	.02	.22	.39*	1.95*	.06	.11	.04	0.15	.00	.07 .20
ICR													
Neutral	.26*	.13	0.60	.00	.21*	.01	0.02	.00	.26*	.15	.65	.08	.08 .20
Emotional Modulation													
Fear	.11	-.12	-0.50	.00	.16	.09	0.44	.00	.16	.20	0.82	.01	.03 .58
Happy	.16	-.10	-0.44	.00	.20	.23	1.14	.01	.20	.12	0.51	.00	.06 .28
Sad	-.04	-.28	-1.16	.02	.05	.11	0.54	.00	.05	.19	0.79	.00	.02 .69

Note. PTSD symptom severity assessed by the IES-R. β = standardised Beta. Unique sr^2 = the semi partial correlation (squared) representing unique variance. * = $p \leq 0.05$, ** = $p \leq 0.01$.

2.1.3 Dimensional Differences in Emotional Modulation to Emotive Images using the Impact of Event Scale-Revised

The IES-R score has also been used to assess unique relationships between the three DSM-IV PTSD subscales and emotionally modulated pupil response. Table B21 shows zero-order correlations and regression statistics for this dimensional analysis. There are significant correlations between all IES-R subscales and the initial constriction response, but no unique contributions of any subscales. However, for the IPD the avoidance scale is a significantly uniquely predictive, suggesting higher avoidance scores uniquely predicted larger IPD, accounting for 6% of the variation in IPD. This result was not found using the CAPS-V avoidance scale (see Table 12) and, as this effect was not hypothesised, it is suggested to be an artefact of multiple comparisons.

2.2 Experiment 2

2.2.1 Average Pupil Dilation to Sound Clips Within the Late (2500 – 3500 ms) Analysis Window

In Experiment One, a reduced initial constriction response was found to be related to PTSD symptom severity using the average pupil size within a 500 ms analysis window during the initial constriction of the pupil. To assess whether PTSD symptoms were related to a general reduction in pupil mobility expressed by a lack of both constriction and dilation, and ANCOVA was conducted within the period of maximal dilation; the 2500 – 3500 ms late window, to neutral sounds in Experiment Two. There was no significant impact of age (p =

.420) nor a main effect of group $F(2, 58) = 1.15$, $p = .323$ indicating no observable deficits in pupil dilation or general mobility.

Appendix C Contrast Sensitivity, Trauma and Personality Disorder: Task Development within a Hospitalised Sample

3.1 Abstract

A defining symptom of Post-Traumatic Stress Disorder (PTSD) is that of 'hypervigilance', with prolonged and sometimes chronic alterations in arousal and reactivity being a hallmark of the disorder. Hypervigilance refers to (1) an enhanced state of sensory sensitivity, and (2) is accompanied by an exaggerated intensity of behaviours that function to detect threat. The present study aims to assess the presence of enhanced sensory sensitivity within a sample of hospitalised personality disorder inpatients, recruited due to elevated traumatic life events within these populations. Participants were both staff and patients recruited from a low secure personality disorder unit in Cardiff. An assessment of visual contrast sensitivity was administered alongside trauma screening questionnaires to assess co-occurrence of trauma symptoms and enhanced sensory sensitivity. Results show that the patient group, despite exhibiting significant symptoms of PTSD, showed comparatively poorer visual contrast thresholds. The results are discussed in terms of the study design and inpatient sample demographic, including: chronic psychotropic medication use and the result of cumulative, complex trauma on physiological arousal.

3.2 Introduction

3.2.1 Post-Traumatic Stress

Post-Traumatic Stress Disorder (PTSD) is a specific response to traumatic events that is characterised by fear and arousal in response to trauma reminders, intrusive thoughts, flashbacks and nightmares about the trauma, and avoidance of reminders of the trauma. The U.S National Co-morbidity Study Replication (NCS-R) reported lifetime prevalence of PTSD among adult Americans to be 6.8% (Kessler, Berglund, et al., 2005). Current past year PTSD prevalence was estimated at 3.5% (Kessler, Chiu, Demler, & Walters, 2005). The lifetime prevalence of PTSD among men was 3.6% and among women was 9.7%, although 60.7% of men and 51.2% of women had been exposed to a traumatic event. The twelve-month prevalence was 1.8% among men and 5.2% among women (National Co-Morbidity Survey, 2005). The incidence of PTSD in traumatic occupations is much higher (Berger et al., 2012) – up to 65% in military troops during Operation Desert Storm, 65% of British ambulance workers and up to 13% of Police Officers. PTSD has a high cost both in human and economic terms. Marshall, Jorm, Grayson and O'Toole (2000) found that a diagnosis of PTSD in a group of Vietnam veterans was associated with medical costs 60% higher than average and Greenberg et al. (1999) calculated the annual economic burden of anxiety disorders, including PTSD, in the USA during the 1990s as $42.3 billion.

A major symptom of PTSD is that of "hypervigilance". Hypervigilance refers to (1) an enhanced state of sensory sensitivity, and (2) is accompanied by an exaggerated intensity of behaviours whose purpose is to detect threat. A cardinal feature of patients with PTSD is sustained hyperactivity of the autonomic sympathetic branch of the autonomic nervous

system, as evidenced by elevations in heart rate, blood pressure, skin conductance, and other psychophysiological measures (McTeague et al., 2010).

3.2.2 Personality Disorder and Trauma

Personality Disorders (PDs) represent a major health challenge. PDs are defined by persistent and enduring problems due to inflexible and maladaptive personality traits. In the UK it is estimated that up to 1 in 5 people have a PD (Coid, Yang, Tyrer, Roberts, & Ullrich, 2006), though most are sufficiently mild that treatment is rarely sought (e.g. only after severe times of stress, such as after recent bereavement). There are many forms of PD (10 distinct types in DSM-IV, retained in DSM-V), but many researchers and clinicians refer to three clusters of PD. There is a notable overlap in symptoms between PTSD and Borderline PD. Both are associated with greater rates of depression, suicide and self-harm substance abuse, impulsive behaviours, problems with anger, and problems with relationships. In Borderline PD there also appears to be "hypervigilance", particularly in the area of relationships where the patients are hypersensitive to, and often actively looking out for, signs of abandonment or rejection (Lynch et al., 2006). There is also abundant evidence that Borderline PD is associated with childhood trauma (McLean & Gallop, 2003) and that those with a diagnosis of Borderline PD are at far greater risk of developing PTSD (Gunderson & Sabo, 1993). Given these similarities, it is not surprising that links have been made between PTSD and PDs (and Borderline PD in particular) with Borderline PD being regarded as a "complex PTSD" (Herman, 1992).

3.2.3 Sensory Sensitivity

See section 4.1.5.

3.3 Method

3.3.1 Participants

The study included two groups comprised of patients and staff at a low secure personality disorder and mental illness hospital in Cardiff, United Kingdom. The patient group was chosen due to the high rates of traumatisation and life adversity in psychiatric samples (Turner & Lloyd, 1995) and a particular abundance of evidence that personality disorder, and borderline personality disorder in particular, is associated with childhood trauma (Gunderson & Sabo, 1993; Herman, 1992; McLean & Gallop, 2003). The patient group consisted of twenty five individuals detained for treatment and carrying diagnoses of ICD-10 (World Health Organization, 1992) /DSM-V (American Psychiatric Association, 2013) primary personality disorder (n =15), mental illness (n =1), personality disorder and mental illness (n =8) and not specified (n =1). Psychiatric diagnoses and medication were obtained from medical records and determined independently by the treating Psychiatrist. Ethical permission to conduct this research was sought from an NHS Research Ethics Committee, and the Responsible Clinician was consulted regarding suitability for research and capacity to give informed consent for each of the patient participants. Participants were eligible to take part if they had normal, or corrected to normal vision and the ability to read and speak the English alphabet. The control group comprised twenty-six age and gender matched controls recruited from the staff population in the hospital. Control participants were recruited via a leaflet in the staff room and eligible to take part if they were not taking any psychotropic medication. All participants were offered monetary compensation for their participation. Demographic features are shown in Table C22, and it can be seen that the two groups did not differ on demographic variables measured other than IQ. It is likely that this

represents a true demographic difference, as the level of educational attainment differed between the groups, with only 12% of patients having attained any formal qualifications (GCSE/O-level, A-Level, NVQ or degree) in comparison to 100% of controls.

Table C22. *Participant Demographics*

	Patient				Control			
Variable	*M*	*SD*	Range	*n*	*M*	*SD*	Range	*n*
Age	33.12	12	19-65	25	34	19.7	20-58	26
IQ [a] **	86	13.2	68-113	23	103	12.4	71-125	26
Sex								
Male				15				16
Female				10				10
Racial or ethnic group								
White British				25				16

Notes. [a] IQ data are unavailable for 2 patients, $^{**}p < .001$

3.3.2 Design

The study employed a cross sectional, quasi-experimental design, with allocation to groups conducted on the basis of psychiatric inpatient or staff status.

3.3.3 Measures

See section 4.1.6.2 for the contrast sensitivity task. All participants were asked to complete clinical and personality measures. Trauma psychometrics were among the most commonly administered measures by traumatic stress professionals (Elhai, Gray, Kashdan, & Franklin, 2005) and included the Post-Traumatic Stress Diagnostic Scale, (PDS; Foa, Cashman, Jaycox, & Perry, 1997), the Post-Traumatic Stress Disorder Checklist-5 (past month version) with extended criterion A assessment and Life Events Checklist-5 (PCL-5 and LEC-5; Weathers et al., 2013) and the Impact of Event Scale-Revised (IES-R; Weiss & Marmar, 1997). The Posttraumatic Stress Diagnostic Scale is a well validated self-report measure of the DSM diagnostic criteria for PTSD, including trauma characteristics, symptom severity and duration, and resultant degree of functional impairment. The PDS has acceptable levels of reliability and validity and shows good diagnostic agreement with the Structured Clinical Interview for DSM–IV (Foa et al., 1997). This tool can also be used to assess whether an individual meets criteria for PTSD, rather than just symptom severity, as it assesses all diagnostic criteria. To be given a positive diagnosis, the traumatic incident needs to meet criterion A, the subject must have symptoms in each domain, which have been present for more than three months, and must also express that they are functionally impaired. The PCL-5 is an updated version of the well validated PCL, as such no validation has been conducted on this instrument as of yet, nor the LEC-5. Internal consistency for the PCL for DSM-IV is very high (Cronbach's Alpha 0.939) (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996). The LEC-5 is a self-report measure designed to screen for potentially traumatic events in a respondent's lifetime. The LEC-5 assesses exposure to 16 events known to potentially result in PTSD or distress and includes one additional item assessing any other

extraordinarily stressful event not captured in the first 16 items. Previous versions of the LEC have been shown to have adequate psychometric properties in both clinical and non-clinical samples (Gray, Litz, Hsu, & Lombardo, 2004). The IES-R is a 22 item self-report questionnaire measuring frequency of symptoms of posttraumatic intrusion, avoidance and hyper-arousal (on separate subscales) over the past seven days. Internal consistency is high (Cronbach's Alpha 0.79 - 0.92) and test-retest reliability is good. The IES-R possesses good validity as a measure of posttraumatic distress, though it should be emphasised that it is not a measure of PTSD diagnostic status. Finally, participants completed a personality psychometric, the Temperament and Character Inventory (TCI; Cloninger, Svrakic, & Przybeck, 1993). The TCI is a 240-item questionnaire, answered on a two-point ('true' or 'false') scale. The TCI measures seven personality dimensions: Novelty Seeking, Harm Avoidance, Reward Dependence, Persistence, Self-Directedness, Cooperativeness, and Self-Transcendence.

Patients gave their consent for the researcher to access medical records in order to ascertain prescribed medication, accepted medication, independent assessment of IQ and psychiatric and medical history.

3.3.4 Procedure

The procedure was carried out in the following order for all participants. The subject was first asked to complete the assessment of visual contrast sensitivity. All participants were instructed to respond by stating aloud which letter of the alphabet they had seen on screen, or to guess if they had not seen a letter. Participants began with 20 practice trials, followed by 100 experimental trials.

Following the assessment of visual contrast sensitivity, all participants completed the clinical measures. The patient group completed clinical and personality measures with the experimenter, and the control group completed these in private. The control group also took part in a short assessment of intellectual functioning, the two subtest Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

3.4 Results

One subject from the patient group was excluded from all further analyses due to disclosure of poor binocular vision after testing and poor completion of all questionnaire measures. None of this individual's data was analysed or scored. Completion rates for all administered measures are displayed in Table C23. Performance decrements in terms of completion were limited to the patient group, with generally poorer completion percentages seen for measures administered later in the testing session. No corrections have been made or dummy variables calculated for missing data. Of note, patients typically declined to complete trauma measures if they reported that they would find this process too distressing i.e. there is likely to be a trend toward missing data representing the more traumatised patients in the sample. In some cases, patients would complete the initial PDS assessment, but then opt out of completing the PCL due to similarity.

Table C23. *Completion Rates for Measures*

	Patient (n = 25)	Control (n = 26)
Measure		
Contrast sensitivity	92% (23)	100% (26)
PDS	88% (22)	100% (26)
LEC-V	80% (20)	100% (26)
Extended Criterion A	88% (22)	100% (26)
PCL-V	56% (14)	100% (26)
IES-R	76% (19)	100% (26)
TCI	75% (18)	100% (26)

Notes. PDS= Post Traumatic Stress Diagnostic Scale, LEC-V = Life Events Checklist for DSM-V, PCL-V = PTSD Checklist for DSM-V, IES-R = Impact of Event Scale-Revised, TCI= Temperament and Character Inventory

3.4.1 Trauma measures

The analysis of the trauma measures (see Table C24) supported previous research (Turner & Lloyd, 1995) in suggesting that the psychiatric patients had experienced more adverse and potentially traumatising life events than the control population. Additionally, the patient group also experienced more of these events directly, as opposed to having witnessed, learnt about, or experienced these as part of a job. Criteria for PTSD were determined via administration of the PDS (Foa et al., 1997). Fifty percent of the patient sample met the criteria for PTSD using this measure, in comparison to eight percent of the control

population. The patient group reported more PTSD symptoms of a greater severity, and seventy three percent of the patient sample endorsed that they are severely functionally impaired as a consequence of the reported trauma, in comparison to one individual from the control population. Final points of interest are the differences between groups on the number of life events that they report to have been equally as stressful as the index event. The patient population showed evidence of repeat traumatisation, reporting an average of seven equally as adverse experiences, but which ranged from one to fifty. This is consistent with the literature on early childhood trauma, complex PTSD and the development of personality disorder (McLean & Gallop, 2003; Pagura et al., 2010; Paris, 1998).

Table C24. *Descriptive Statistics for Trauma Measures*

Measure			Patient ($N = 25$)	Control ($N = 26$)
LEC-V				
	Total trauma events**		11.9 (6.73)	7.16 (4.2)
	Direct trauma events***		5.04 (2.06)	1.61 (1.23)
PDS				
	PTSD diagnosis**			
		Yes	50% (11)	8% (2)
		No	36% (8)	85% (22)
		Incomplete	14% (3)	8% (2)
	Total symptoms***		10.22 (5.25)	3.76 (3.98)
	Functional impairment***			
		None	23% (5)	88% (23)
		Mild	5% (1)	4% (1)
		Moderate	0% (0)	4% (1)
		Severe	73% (16)	4% (1)
PCL-V, Extended Criterion A Assessment				
	Similar experiences**		6.95 (10.75)	1.32 (0.98)
	Months since event**		178.47 (86.48)	132.60 (117.27)
IES-R				
	Symptom total***		35.26 (23.91)	12.42 (14.03)

Notes. Where means are reported, the number in brackets reports standard deviation. Where frequencies are reported, these are expressed as a rounded percentage and the number in brackets represents frequency total. * $p \leq 0.05$, ** $p \leq 0.01$, ***$p \leq 0.001$

3.4.2 Group analysis

An independent samples *t*-test on contrast thresholds at peak sensitivity revealed that there was a significant difference in the threshold scores in the patient (M = .0137, SD = .005) and control (M = .0103, SD = .005) groups; $t(47) = 2.45$, p = .018, Cohen's d = 0.71. Contrary to the hypothesis, this suggests that the patient group showed generally poorer visual sensitivity. The distribution of contrast detection thresholds is shown in Figure C24.

Shapiro-Wilk tests for normality indicate the distribution of visual threshold data in the control (S-W = 0.936, df = 26, p = 0.109) and patient (S-W = 0.932, df = 23, p = 0.122) groups to be within acceptable bounds. However, it is apparent that the skew of the distribution in the patient group is greater, with skewness value of 0.983 (SE = 0.481) and kurtosis of 2.21 (SE = 0.935) in comparison to the control group, which had a skewness value of -0.502 (SE = 0.456) and kurtosis of -0.896 (SE = 0.887). Removal of the two most outlying values in the patient group corrected this kurtosis value to 0.1 (SE = 0.97). An independent samples t-test on these corrected values revealed this difference to be marginally significant ($t(44) = 1.63$, p = 0.067). It is therefore possible that the difference between groups is represented by a confounding variable within the patient population, leading to extremely detrimental performance that was outside of the normal distribution, as was the case in these two outlying values. One such confounding variable not present in the control group is likely to be psychotropic medication, or a side effect of medication use, such as global sedation (see appendix on medication below). It is possible that these two outliers showed the most impairment due to medication levels.

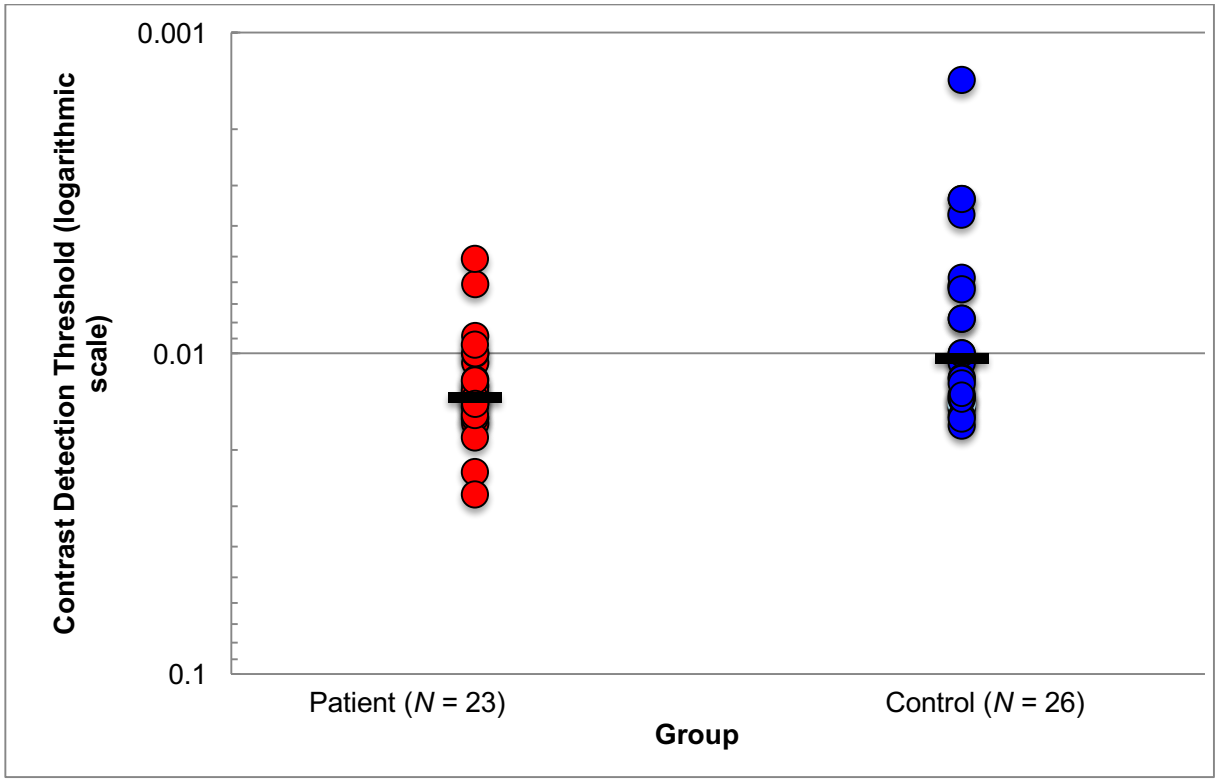

Figure C24. Distribution of Contrast Detection Thresholds Between Patient and Control Groups.

The contrast detection threshold is defined by the ratio of the difference between the maximum and minimum luminance of the letter optotypes, divided by the sum of these two quantities and represented on a logarithmic scale. The horizontal bars represent the mean of each group distribution, and the circles represent individual data points. Greater scores indicate greater thresholds for detection and poorer performance.

3.4.3 Medication

Impairments in visual contrast sensitivity have been linked to the type of antipsychotic medication administered. Chen et al. (2003) suggest that first generation,

typical antipsychotic medications produce visual sensitivity impairments, whereas second generation atypical antipsychotic medications do not and, moreover, that this difference is due to the mechanism of pharmacotherapy. Within the patient group, eighty five percent of individuals were prescribed an antipsychotic medication, representing the most frequently prescribed class of drugs in this sample. Figure C24 represents the differences in contrast sensitivity thresholds according to class of antipsychotic medication in those patients whom had accepted one or more prescribed doses in the past 48 hours. This method of assessment (accepted doses in the past 48 hours, rather than prescribed medication) was chosen since patients can be non-compliant with some doses of medication.

Table C25. *Psychotropic Medication Use in the Patient Sample*

Medication type	(*N* = 23)	
Analgesic, opiate form	17%	(4)
Anti-anxiety	56%	(13)
Anti-depressant	43%	(10)
Anti-psychotic		
Typical	47%	(11)
Atypical	21%	(5)
Both	17%	(4)
Mood stabilising	17%	(4)
Other and non-psychotropic	52%	(12)

Note. Frequencies are expressed as a rounded percentage and the number in brackets represents frequency total.

The difference in group sizes and small, unplanned samples mean that inferential statistics have not been calculated. Nonetheless, as can be seen from, the individuals with the lowest detection thresholds also belong to the typical antipsychotic group, and these are the only individuals who fall outside of the range of thresholds from the control group. However, it is not possible to draw clear conclusions from medication statistics in this population due to the lack of controlled administration. The two individuals with the highest thresholds were also in receipt of opioid analgesic medication (Tramadol, Oromorph), anti-anxiety medication (Lorazepam, Diazepam and Temazepam) and other medications for general health. It is unclear how visual sensitivity is affected by chronic use of these agents, by the interactions between them, individual metabolism or time since administration. It is clear from the research literature that psychotropic medications have effect in the visual system (see

Appendix A for a review), and individuals in receipt of such medication are likely inappropriate for visual research in which they are being compared to a non-medicated sample.

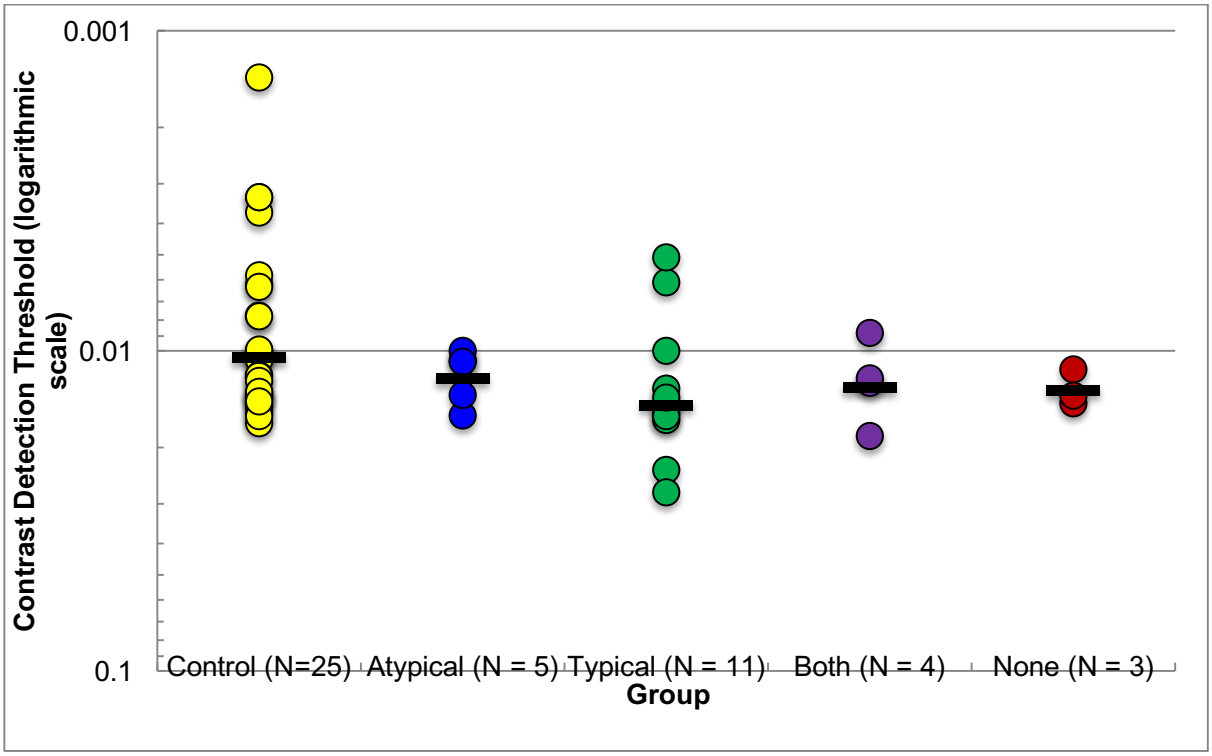

Figure C25. Distributions of Contrast Detection Thresholds within the Sample Populations by Anti-Psychotic Medication type.

3.4.4 Analysis by PTSD Criteria

Within the current study, to address the complications due to administration of psychotropic medications, separate analysis has been conducted within the patient group alone. Those meeting criteria for PTSD were determined via the PDS (Foa et al., 1997), as this was the measure with the highest completion rates and can be used as a diagnostic screening tool (see Table C23).

The distribution of the contrast thresholds by PTSD status are represented in Figure C26. Without exclusions, an independent samples t-test on contrast thresholds at peak sensitivity revealed that there was a significant difference in the threshold scores in the PTSD positive (M = .0111, SD = .0036) and negative (M = .0158, SD = .0055) groups; $t(19)$ = 2.357, p = .029, Cohen's d = 1.017. This indicates that the PTSD positive group showed significantly lower contrast thresholds and thus showed greater visual sensitivity.

When accounting for two outlying values identified above, the difference between the PTSD positive (M = .0111, SD = .0035) and PTSD negative (M = .0134, SD = .0019) groups were non-significant ($t(17)$ = 1.636, p = 0.12). Consideration of the demographic factors of these two groups also revealed unequal matching in terms of both gender and age. The PTSD positive group consisted of seven females and four males, with an average age of 31.6. The PTSD negative group consisted of one female and ten males, with an average age of 36. Although the ages of the group were not significantly different (p = 0.357), the gender difference between the two groups may be representative of the higher prevalence of borderline personality disorder, and associated complex PTSD in females.

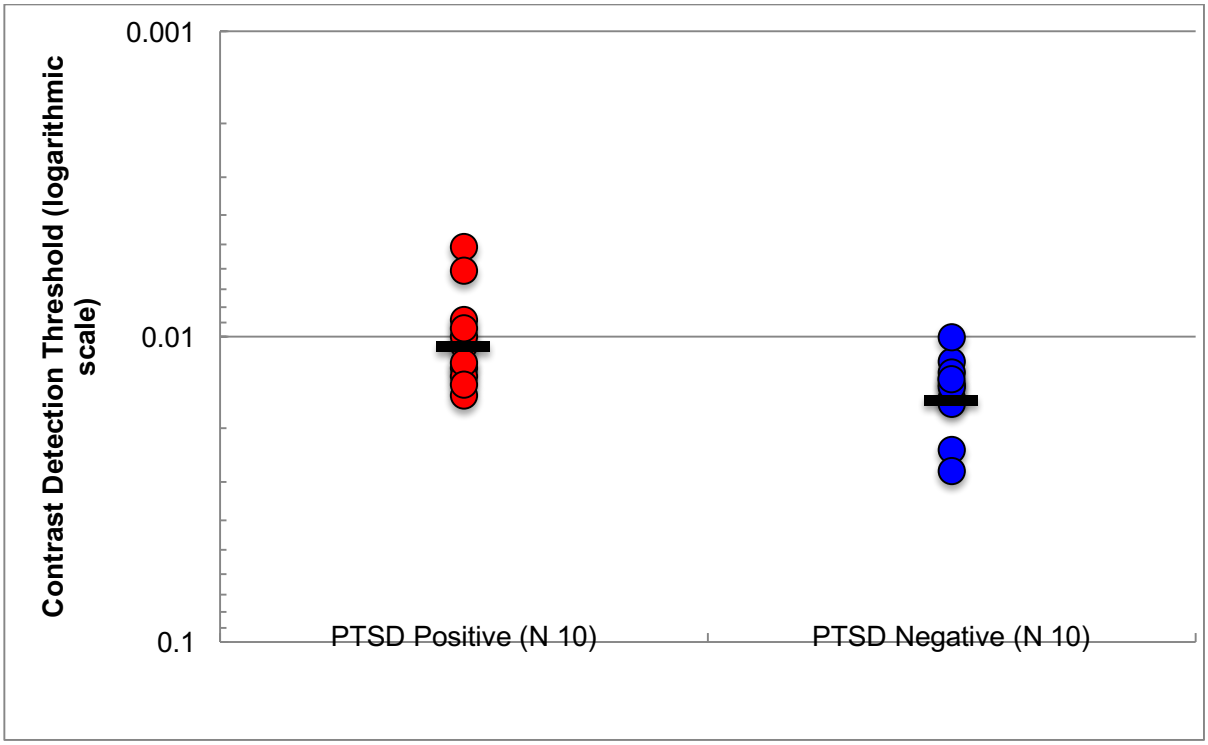

Figure C26. Distributions of Contrast Detection Thresholds Within the Patient Population by PTSD Criteria. The horizontal bars represent the mean of each group distribution, and lower scores represent lower detection thresholds.

3.4.5 Gender

Due to the significant demographic difference in terms of gender within the PTSD positive and negative groups, a literature search was conducted in the area of sex differences in contrast sensitivity. The only relevant study that was found was conducted by Brabyn and McGuinness (1979), whom assessed contrast sensitivity functions for both males and females, and found females to show greater sensitivity at low spatial frequencies for static gratings. Follow up work in this area is sparse, and has largely focussed on reaction times (e.g., Solberg & Brown, 2002). In the current study, with two outlying patients excluded, there was no significant difference between females (M = 0.0103, SD = 0.0046) and males (M = 0.0123, SD = 0.0033) $t(45) = 1.645$, $p = .107$.

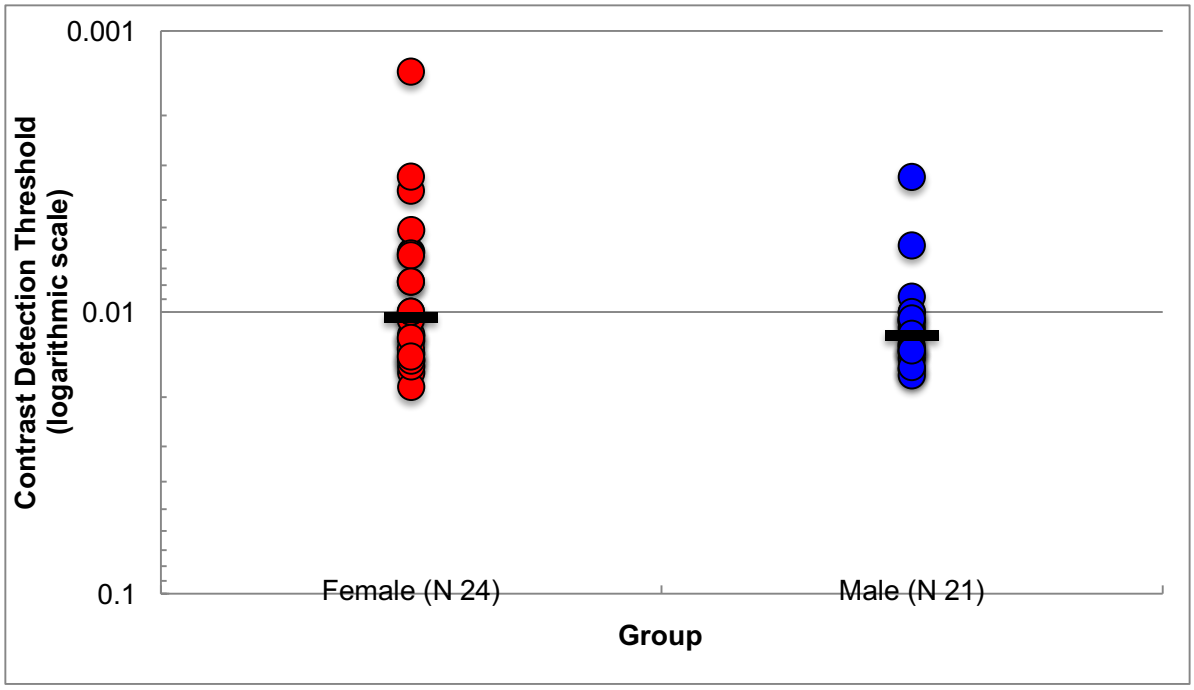

Figure C27. Distributions of Contrast Detection Thresholds within the Sample Populations by Gender. The horizontal bars represent the mean of each group distribution, and lower scores represent lower detection thresholds and greater sensitivity.

3.4.6 Test–Retest Reliability

For patient subjects, the test–retest reliability of the CSF threshold parameter obtained with the letter contrast method was evaluated for a random subset of 10 patients. This was done to assess reliability in a psychiatric population, where these assessments have not been carried out before, and also to rule out practice effects, inattention effects, and to assess the robustness of this measure within a medicated sample. Ten individuals from the patient sample were recruited 7 days later to repeat the letter contrast assessment. One patient declined reassessment so the next individual was selected at random. Pearson correlations between thresholds measured in the first and second sessions were calculated. The test–retest

correlation was good, (r = .72, p = <.05). Four individuals in the sample demonstrated a decline in performance from test time one and six individuals improved. A t-test revealed there was no significant tendency toward either improvement or decline in visual threshold ($t(18) = 0.19$, p = .85) suggesting that this assessment within this sample is not vulnerable to practice effects one week later.

3.5 Discussion

The present study aimed to pilot the assessment of visual contrast sensitivity as a possible index of hyper-vigilance trauma symptoms in a sample of patients from a personality disorder unit. The results revealed that participants being detained for treatment in a low secure psychiatric hospital had experienced more potentially traumatic life events than a control sample of staff, and demonstrated higher rates of Post-Traumatic Stress Disorder diagnoses, symptom severity and functional impairment. The assessment of visual contrast threshold suggested that patients demonstrated significantly poorer visual sensitivity, contrary to the hypothesis. There are several possible explanations for this finding. The first candidate, as discussed above, being levels of psychotropic medication use within this sample. The eye has been shown to be the second most frequent organ to manifest drug toxicity, after the liver (Li et al., 2008) and previous work isolating the effects of an acute dose of psychotropic medication on visual contrast sensitivity paints a complex picture of their effects on the visual system. Whilst the great majority of evidence points to visual impairments due to medications, the reasons for these impairments are difficult to separate (i.e., is this due to sedative side effects, or a true impact on a visual channel), and no research has addressed the varying combinations as well as the chronic use of these drugs which were present in this sample.

The patient subjects recruited violate many of the usual exclusion criteria for visual experimentation and, in addition to prescription medication, eighty percent of the sample had been independently assessed as having a history of severely problematic substance misuse or dependency. These two factors allude to the complexity and severity of the mental health of the patient group in question and speak to the limited amounts of empirical research conducted within this sample, at least when the research is looking at performance measures. If this type of research is unavoidable, the best practice would be to match subjects in order to compare individuals on similar medication regimes to one another (a within patients design), rather than using a non-medicated control group.

The second potential confound to this study is the complexity and heterogeneity of the trauma-related symptom cause and effect within this patient population. Research by McTeague et al. (2010) assessed the physiological response variation in participants who had suffered singular-trauma PTSD versus multiple-trauma PTSD. Despite greater reported arousal, the multiple-trauma relative to single-trauma group showed blunted defensive reactivity associated with more chronic and severe PTSD, greater mood and anxiety disorder comorbidity, and more pervasive dimensional dysphoria (e.g., depression, trait anxiety). This result is surprising, given that autonomic and somatic arousal are hallmark symptoms of PTSD across varied trauma acquisition types (S. P. Orr et al., 1993; Pitman et al., 2001, 1987; e.g., Shalev et al., 1993). A review by Pitman et al. (2001) combined the results of physiological response across multiple samples. They estimated that 30-40% of participants with PTSD were physiologically non-responsive during trauma-related processing. This suggests either that there are additional confounding factors present in these individuals, or, possibly, that the physiological responsivity and symptom severity do not operate in a linear, dose-response fashion. This type of curvilinear relationship would be predicted by the

Pavlovian concept of transmarginal inhibition (in Gray, 1964, see Figure 18) or some interpretations of the Yerkes-Dodson inverted-U relationship between anxiety and performance (Yerkes & Dodson, 1908, but see Teigen [1994] for a review of interpretations). This kind of non-linear dose-response relationship can be seen in other areas of science, such as the toxicological concept of hormesis. In terms of toxicology, hormesis implies that low doses of potentially toxic substances produce stimulation, whereas high doses produce inhibition/death (Stebbing, 1982). In this instance, low doses of arousal or vigilance stimulate the system to respond to threat, whereas high doses of arousal could be seen to inhibit the defensive systems. Pavlovian personality theory predicts that once the organism has passed beyond the point of transmarginal inhibition, behaviour ceases to hold adaptive function (the 'ultra-paradoxical phase').

In sum, the evidence for chronic dysregulation of physiologic responding in complex PTSD and the most chronic of trauma cases suggest that this population, or this cross-sectional methodological approach, is not the most appropriate to test this hypothesis. A more appropriate sample would involve 'simple' or singular trauma PTSD, an unmedicated sample, or, ideally, a prospective sample.

Appendix D Analysis Script for Pupil Data

4.1 Rationale and Access

Analysis of data from pupillometry studies is complex and time consuming. With a 60Hz data collection rate within a 6-minute experimental paradigm 21,600 pupil diameter measurements are collected per participant. The analysis script used herein was written by in Python using NumPy and Pandas extensions by Aimee McKinnon and Adam Price. The software is available from a GitHub repository on request from the authors, free of charge. Request the requirements, licence and main analysis script from aimee.mckinnon@me.com.