Personality and Attention Bias in Adults with a History of Childhood Trauma, and Attenuating Effects of mu-Opioid Agonist Buprenorphine on Attention Bias

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A dissertation submitted in fulfilment of the requirements for the award of the degree of Master in Psychological Research

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COMPULSORY DECLARATION

This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Each significant contribution to, and quotation in, this dissertation from the work, or works, of other people has been attributed, and has been cited and referenced.

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ABSTRACT

The current study compared personality characteristics and cognitive functioning (specifically, attentional bias) in a sample of adults who had experienced childhood trauma (the Trauma group) and a matched healthy control group. The study also examined the possible effects of the mu-opioid agonist buprenorphine on attentional bias in the Trauma group. As a preliminary step, the first objective explored in the current research was to examine the test-retest reliability of the childhood trauma questionnaire-short form (CTQ-SF; Bernstein et al., 2003), an instrument for which no test-retest reliability data is currently available. The CTQ-SF was administered to the sample on three separate occasions.

Following this preliminary step, the next set of objectives explored in the current research involved three specific hypotheses: *Hypothesis 1* stated that, with regard to behavioral inhibition system (BIS) and behavioral approach system (BAS) sensitivity, I predicted that adults with a history of childhood trauma would have heightened activation of the BIS. This increased BIS activity would, I predicted, be reflected in relatively higher scores on the BIS dimension of Carver and White's (1994) BIS/BAS scale. No significant differences were predicted for BAS sensitivity. *Hypothesis 2* stated that, with regard to performance on the Object Relocation Task, adults with a history of childhood trauma would demonstrate an information-processing bias for threat-related stimuli and avoidance of approach-related stimuli, reflected in significantly less error for relocating fearful faces to their original locations and more error for relocating angry and happy faces to their original locations, compared to healthy matched controls. *Hypothesis 3* stated that buprenorphine would alleviate the attentional bias for fearful faces described above.

The data presented in this thesis showed that, as a measure of childhood trauma, the CTQ-SF generated good test-retest reliability on four of its five subscales over variable lengths of time, even given different methods of survey delivery across administrations. In addition, I found that participants with a history of childhood trauma did not differ from matched controls with regard to the current study's indices of behavioral approach and inhibition, and with regard to attentional bias. Furthermore, buprenorphine demonstrated no observable alleviation of attentional bias in individuals with histories of early adversity. One possible explanation for the lack of between-group differences may be related to the moderate severity of adverse experiences reported by the Trauma group.

INTRODUCTION

The lifetime prevalence of exposure to a traumatic stressor (with "stressor" taken as defined by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association [APA], 1994)) is approximately 90% (Breslau et al., 1998). This epidemiologic statistic suggests that a great majority of people will be subjected to an experience that will elicit "intense fear, helplessness, or horror" (Criterion A2 of the DSM-IV description) at one time or another throughout the course of our lives. For a subset of individuals, such a traumatic event will occur during childhood. A recent estimate for the prevalence of exposure to a traumatic stressor in childhood (i.e., up to 16 years of age) is approximately 67% (Copeland, Keeler, Angold, & Costello, 2007). This figure is particularly alarming given the vulnerability of the developing brain to severe stressors.

During sensitive developmental periods in early life, the human brain may be particularly vulnerable to the effects of traumatic stressors. The neurophysiological effects of early childhood adversity are thought to predispose the young brain to develop along a pathway that is particularly sensitive to stress. For example, prolonged maternal separation in early life may produce a flooding of neurotransmitters and hormones which could affect myelination, neural morphology, neurogenesis, synaptogenesis, and additionally cause alterations in molecular organization in the young brain, which may lead to enhanced fearfulness and anxiety (Teicher, Andersen, Polcari, Anderson, & Navalta, 2002). Such alterations have the effect of predisposing the individual to a range of psychiatric and cognitive disorders (Teicher et al., 2003).

A meta-analysis ($N = 77$ separate empirical studies) found that the experience of early life trauma was a significant risk factor for the onset of posttraumatic stress disorder (PTSD) in later life (Brewin, Andrews, & Valentine, 2000). In a study examining four successive birth cohorts dating back to 1900, Dube, Felitti, Dong, Giles, and Anda (2003a) found a significant association between adverse childhood experiences and increased risk for depressed affect, suicide attempts, multiple sexual partners, sexually transmitted diseases, smoking, and alcoholism. Childhood trauma has also been linked to increased risk for, in adults, depressive disorders (Chapman et al., 2004), bulimia nervosa (Wonderlich et al., 2007), illicit drug use (Dube et al., 2003b), obsessive-compulsive disorder (Mathews, Kaur, & Stein, 2008), and a range of personality disorders (Johnson, Cohen, Brown, Smailes, & Bernstein, 1999; Sansone & Sansone, 2007).

The current study compares the personality characteristics and cognitive functioning (specifically, attentional bias) in a sample of adults who have experienced childhood trauma and a matched healthy control group. The study also examines the possible effects of the mu-opioid agonist buprenorphine on attentional bias in the Trauma group. Mu-opioids are associated with the attenuation of emotional and affective physiological responses to stressors (Drolet et al., 2001) and may therefore have a dissipating effect on the fear response in individuals with elevated levels of anxiety (Panksepp, 2003), a trait that is commonly associated with individuals who have experienced early adversity.

Personality Characteristics of Adult Survivors of Childhood Trauma

In a prospective longitudinal study investigating the effects of early adversity on development of personality disorders in early adulthood, the experience of childhood abuse and neglect was found to quadruple the likelihood of having a personality disorder in early adulthood (Johnson et al., 1999). This finding remained significant after the effects of age, parental education, and parental psychiatric disorders were statistically controlled for in a sample of individuals with (n = 31) and without (n = 608) a history of childhood abuse and neglect. In addition, when looking at abuse and neglect separately, the authors found physical abuse to be associated with increased antisocial and depressive personality disorder symptoms; sexual abuse to be related to increased borderline personality disorder symptoms; and neglect to be associated with increased symptoms of avoidant, antisocial, borderline, narcissistic, and passive-aggressive personality disorders. Finally, being diagnosed with any one of 10 of the 12 personality disorders listed in the DSM-IV was associated with the experience of any form of childhood abuse or neglect.

This seminal study highlighted a significant association between the experience of childhood adversity and the diagnosis of a personality disorder in adulthood. Its findings have largely been supported by subsequent research. For instance, Rojas and Pappagallo (2004) found that childhood histories of sexual and physical abuse were risk factors for the development of borderline personality disorder, antisocial personality disorder, and major depression during adulthood. Similarly, Sansone and Sansone (2006) identified significant associations between early adversity (e.g., physical abuse, emotional abuse, sexual abuse, physical neglect, etc.) and borderline, antisocial, paranoid, avoidant, and schizotypal personality disorders.

The experience of childhood trauma does not, of course, invariably result in the development of a DSM personality disorder during adulthood. However, by showing the increased presence of maladaptive personality traits in childhood trauma victims compared to healthy participants, the above studies emphasise the elevated risk that victims of childhood trauma have for developing disordered personalities during adulthood. Before moving further into the literature review, and in order to move the discussion away from DSM-defined personality disorder, it is useful to describe what psychological researchers mean when they refer to "personality traits". A general definition of this concept holds that they represent stable, characteristic ways of thinking, feeling, and regulating affect within the individual (Daud, af Klinteberg, & Rydelius, 2008). Hence, personality traits ultimately determine the way an individual experiences the world.

A trait that has consistently been associated with victims of early life stress is neuroticism (Allen & Lauterbach, 2007; Bunce, Larsen, & Petersen, 1995; Glaser, van Os, Partegijs, & Myin-Germeys, 2006; Lysaker, Meyer, Evans, Clements, & Marks, 2001; McFarlane et al., 2005; Rosenman & Rodgers, 2006; Roy, 2002). *Neuroticism* is characterised by the chronic experience of negative affective states, such as depressed mood and anxiety, and a vulnerability to environmental stressors. Individuals high in neuroticism react more negatively to stress, and are thus more likely to interpret ordinary everyday scenarios as dangerous or threatening (Roy, 2002).

In line with these observations, Glaser et al. (2006) found that neuroticism was significantly related to the experience of daily life stress in adult victims of childhood trauma. Individuals high in neuroticism have also been found to be at increased risk for internalizing mental disorders (Clark, Watson, & Mineka, 1994). This latter term refers to conditions of internalized anxiety, such as phobias, panic disorder, depression, and other anxiety disorders. Externalizing disorders, in contrast, are behavioural disorders characterised by impulsivity or disinhibition, such as, attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (Brenner, Beauchaine, & Sylvers, 2005; Daud et al., 2008).

Other adult personality traits associated with the experience of childhood trauma are decreased conscientiousness and increased openness (Allen & Lauterbach, 2008; McFarlane et al., 2005). Interestingly, the findings of increased openness (i.e., openness to new experiences; curiosity; creativity; open-mindedness) in this population are initially counterintuitive when one

considers the neurotic traits of childhood trauma victims. However, Allen and Lauterbach (2008) argue that openness may lead to risky behaviours that make the trauma victim vulnerable to repeated exposure to trauma. A more optimistic view is shared by McFarlane et al. (2005), who state that the trait of openness might be an adaptation to the environmental stressors experienced in the trauma population.

Research into adult personality traits associated with childhood trauma is currently scarce, but has gained momentum in recent years. In a long-term longitudinal study using randomly selected samples of adults in Australia (N = 7485), researchers investigated the effects of childhood adversity on multiple adult personality characteristics. The authors examined neuroticism, extraversion-introversion, psychoticism, behavioural inhibition and activation, and positive or negative affectivity (Rosenman & Rodgers, 2006).Findings showed adverse childhood experiences to significantly increase the risk of high neuroticism (odds ratio (OR) = 2.6), negative affect (OR = 2.6), behavioural inhibition (OR = 1.7), and dissocial behaviour (OR = 1.7) in adult life. No significant effects were found for extraversion, psychoticism, or behavioural activation.

BIS/BAS. The model of personality investigated in this research is the behavioural inhibition and activation system developed by Gray (1981, 1982). According to this model, the behavioural inhibition system (BIS) and the behavioural activation system (BAS) represent two distinct neural systems that mediate the motivational impulses of aversion and appetite, respectively. The bi-directional nature of the systems proposed in Gray's model represents two dimensions of personality, namely, anxiety proneness (mediated by the BIS) and impulsivity (mediated by the BAS) (Carver & White, 1994).

With regard to the neural bases of the BIS, it is proposed to encompass the amygdala and septo-hippocampal system, its monoaminergic afferents from the brain stem, and its neocortical projection to the frontal lobe (Gray, 1977, 1981, 1990). BIS activation controls the experience of anxiety in response to threatening stimuli, and may also underlie feelings of fear, anxiety, and sadness in response to threatening cues. Individuals with greater BIS sensitivity are thought to be more prone to anxiety when confronted with threatening cues (e.g., punishment, nonreward, and novelty) (Brenner et al., 2005; Carver & White, 1994).

With regard to the neural bases of the BAS, it is mainly represented by catecholaminergic (and especially dopaminergic) pathways running through the ventral tegmental area and the

nucleus accumbens of the ventral striatum (Gray, 1981, 1987, 1990). Activation of this system controls goal-directed behaviour, and may also be responsible for the experience of positive emotions such as hope, elation, and happiness. Individuals with greater BAS sensitivity are said to be more prone to engage in goal directed behaviour and to experience positive feelings when exposed to cues of impending reward (Carver & White, 1994; Brenner et al., 2005).

In addition, Gray's model proposes that the two systems are neurobiologically arranged in a distinct manner so that no interaction exists between them. Sensitivity in BIS is therefore not related to sensitivity in BAS, and vice-versa. Studies investigating BIS/BAS activation typically use Carver and White's (1994) BIS/BAS scales to measure sensitivity along the separate dimensions. Consistent with the independent nature of the systems, researchers often find significant effects on one of the dimensions (e.g., BIS; Rosenman & Rodgers, 2006) and not the other, or make predictions on only one of the dimensions (e.g., BAS; Harmon-Jones & Allen, 1997). Researchers have examined numerous disorders associated with variations in the sensitivities of both the BIS and BAS, individually and in combination.

Research suggests that heightened BIS activity, as measured by the BIS/BAS scales (Carver & White, 1994), is significantly associated with clinical levels of anxiety (Vervoort et al., 2010). Similarly, decreased BIS activation is associated with the type of disinhibition observed in ADHD (Quay, 1997). Under-activation in both the BIS and BAS, resulting in sensation-seeking behaviours, may be associated with behavioural symptoms typical of conduct disorder (Beauchaine, Katkin, Strassberg, & Snarr, 2001). Low BAS activity, resulting in a lack of positive experiences and expectancies, is related to the anhedonic symptoms of depression (Beevers & Meyer, 2002). Finally, heightened BAS activity, which is associated with increased reward responsiveness and risk-taking behaviours, has been linked to substance abuse and addiction (Franken, Muris, & Georgieva, 2006; Loxton & Dawe, 2001).

There is a paucity of research investigating the behaviour inhibition and activation personality traits in adults with a history of childhood trauma. An understanding of these traits could have important clinical and pharmacological implications for the treatment and prevention of disorders associated with childhood trauma (Ballenger et al., 2004). However, findings suggest that higher levels of adverse childhood experiences significantly increase the risk of higher BIS sensitivity, with no significant relationship between childhood adversity and BAS (Rosenman & Rodgers, 2006). Such findings are to be expected given the relationship between

childhood trauma and anxiety-related personality traits such as neuroticism (see, e.g., Allen & Lauterbach, 2007; McFarlane et al., 2005; Rosenman & Rodgers, 2006), and given the fact that heightened BIS activation is associated with an increase in symptoms of anxiety (Vervoort et al., 2010).

The development of maladaptive personality traits in victims of childhood trauma. An important issue in research into the personality characteristics associated with childhood trauma is whether those characteristics are a consequence of the effects of early stressors on neurodevelopment, or whether they represent a pre-existing vulnerability to stress that intensifies the experience of traumatic events and thereby predisposes individuals to subsequent psychiatric and psychological disorders (Daud et al., 2008). Researchers are largely in agreement that despite potential pre-existing vulnerabilities to stress, repeated traumatic stress in childhood results in a cascade of neurodevelopment changes that directly influence subsequent adult personality characteristics (Ballenger et al., 2004; Perry, Pollard, Blakley, Baker, & Vigilante, 1995; Teicher et al., 2002; Teicher et al., 2003). What is still at question, however, is the degree to which innate characteristics interact with experience to result in stable personality dispositions. For some investigators, the interaction does not lend itself to resolution, and they therefore take the position that research should focus on clarification, rather than resolution (Rosenman & Rodgers, 2006).

Perry et al. (1995) suggest that traumatic experiences in childhood result in neurophysiological changes in the developing brain that, through repeated exposure, manifests in stable traits. The neural systems within the young brain do not all develop at an equal pace. Different systems undergo organization and differentiation at different times, during which they either require (critical periods) or are more sensitive to (sensitive periods) external environmental and internal neurochemical cues. Disruption of these critical cues may result from sensory deprivation during these periods, or from exposure to extreme stressors (e.g., traumatic experiences) and resultant abnormal neuronal activation. Once severe disruptions occur within critical or sensitive periods, the developing brain becomes particularly vulnerable to develop later psychopathology. For Perry et al., (1995), the mechanisms leading up to this state of vulnerability are defined by internalization of sensitized neurobiological states.

Neurobiological systems are “use-dependent”, meaning, the more a system is activated, the more that state of activation (e.g., calm, fear, sleep) becomes entrenched in memory. The

neural system becomes sensitized to the stimuli that recurrently trigger it. Once sensitized, decreasingly intense stimuli become able to activate the same neural system. The system thereby becomes hypersensitive to those stimuli and the state of arousal thus becomes entrenched, that is, it becomes a trait marker of the individual. For Perry et al. (1994), those personality traits in victims of childhood trauma fall on two dimensions, namely, hyperarousal (what they call an internalized fight or flight stress response) and dissociation (what they call an internalized freeze and surrender stress response). These traits reflect initial response patterns to stressors that become pathological after repetitive stimulation through sensitization. Sensitization is primarily an adaptive response to external stimuli. However, in the case of trauma, repetitive or prolonged exposure may become maladaptive. Experiences during the critical developmental periods of early life may therefore inform the organization of brain systems. The use-dependent changes in neurodevelopment and organization predispose the victim of childhood trauma to a range of emotional, behavioral, cognitive, social, and physiological alterations (Perry et al., 1995).

Teicher and colleagues (2002, 2003) express a very similar conceptualization of the course of neurodevelopment after traumatic experiences in the young brain. They state that a cascade of neurophysiological effects brought on by severe stress during sensitive or critical developmental periods in childhood predispose the young brain to develop along a stress-responsive pathway that makes the individual vulnerable to high stress reactivity. This neurodevelopmental change may increase the possibility of cognitive disruption, such as a bias in information-processing.

Information-Processing Bias in Adult Survivors of Childhood Trauma

Information-processing bias refers to a bias in the way individuals process stimuli from the environment around them. Within the research setting, researchers may use emotionally-laden words, or faces displaying various emotional reactions, as stimuli to investigate such bias. In such research contexts, an information-processing bias occurs when people attend to one type of emotion more than to another. Thus, some people may show a bias towards happy faces, and therefore spend more time attending to and focusing on those faces. Information processing requires attention, inhibition, and working memory and is therefore dependent on the executive control system, located in the pre-frontal cortex (PFC; Arnsten & Li, 2005). Furthermore, the

amygdala is uniquely implicated in the processing of emotional stimuli and the formation and recollection of emotional memory (McGaugh, 2000; Rolls, 2000; Teicher et al., 2002).

Researchers have been able to identify various patterns of information-processing biases associated with specific psychiatric diagnoses. For instance, individuals with a diagnosis of PTSD have a specific bias towards threatening stimuli when compared to matched healthy controls (Dalgleish, Moradi, Taghavi, Neshat-Doost, & Yule, 2001; Moradi, Taghavi, Neshat-Doost, Yule, & Dalgleish, 1999). These biases are fairly robust across cognitive processes (e.g., memory, attention, etc.) and stimuli form (e.g. words, faces, pictures, etc.; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenberg, & Ijzendoorn, 2007).

Research into attentional bias related to emotional stimuli stems from earlier investigations of temperaments and individual affective traits, in particular positive and negative affective traits. This research highlights asymmetrical brain activation associated with the quality of individual affective traits. Findings show, by and large, that processing of positive affective traits is associated with activation in the left frontal brain region, whereas that of negative affective traits is associated with activation in the right frontal region (Davidson, Jackson, & Kalin, 2000). Additional findings link positive emotional processing to left frontal activity, and negative emotional processing to right frontal activity. Together, these findings led to the conceptualization that the left frontal region only processes positive emotions, whereas the right frontal region only processes negative emotions (Heller, Nitschke, & Miller, 1998). Furthermore, researchers considered behavioural motivational direction (approach and avoidance/withdrawal) to be synonymous with emotional valence (i.e., approach tendency regarded as positive; withdrawal tendency is regarded as negative). This theoretical framework has come to be known as the *affective valence hypothesis* (Harmon-Jones, 2004).

The affective valence hypothesis may lead to ambiguity in the outcomes and interpretation of findings in information-processing research. Specifically, in accordance with the hypothesis, researchers examining emotional-processing bias group their stimuli according to their relative affective valence. Hence, for instance, aggressive and fearful stimuli would be grouped as threatening (negative in valence; e.g., Bar-Haim et al., 2007; van Honk et al., 1998;). One reason this strategy can be considered problematic is outlined by proponents of the *motivational direction hypothesis* of emotional processing.

The motivational direction hypothesis posits that emotional information is not processed according to the valence of the stimulus, but rather that it is the tendency of the stimulus to provoke an approach- or avoidance-related response that determines its subsequent processing (Harmon-Jones, 2004). Evidence for this hypothesis comes from the observation that anger has the unique characteristic of being negative in valence while evoking approach motivation. Furthermore, findings demonstrate that anger is not processed in the right frontal brain region, but that processing of aggression occurs in the left frontal region (Pizzagalli, Sherwood, Henriques, & Davidson, 2005; van Honk & Schutter, 2006). There is a growing body of research that supports the motivational direction hypothesis (see, e.g., Heuer, Rinck, & Becker, 2007; van Honk et al., 1998, 2003; Pizzagalli et al., 2005; Putman, Erno, & van Honk, 2007). Pathology associated with bias towards approach-related stimuli (i.e., anger) may therefore produce different trends in attentional biases when presented with avoidance-related stimuli (i.e., fear). This is why it can be considered problematic to group aggressive and fearful stimuli together: they evoke responses in different motivational directions.

Research into information-processing bias relies on a range of methodological paradigms. There is variation in the types of tasks used to elicit a processing bias; the types of stimuli presented; and the way in which stimuli are presented (see Bar-Haim et al., 2007). All of these design variations make cross-study comparison and evaluation difficult. Variation with regard to stimulus presentation may influence the validity of findings in emotional processing. This variation most often exists along these dimensions: the emotional stimulus is either presented under conditions that preclude conscious processing (unconscious/subliminal exposure), or under conditions that allow it to be consciously perceived (supraliminal exposure).

The processing of emotional stimuli may yield different (or even opposite results) depending on whether those stimuli are presented subliminally or supraliminally (Bar-Haim et al., 2007; van Honk et al., 1998). One possible explanation for such confusing patterns of results is this: It is possible that participants are able to exert conscious control over task performance in emotional-processing paradigms. Under the motivational direction hypothesis, high levels of anxiety are associated with attentional bias toward fearful stimuli and an avoidance of angry and happy stimuli. In subliminal exposure paradigms, these trends would remain as expected. However, in supraliminal exposure paradigms, anxious participants may consciously control task performance through avoidance of fearful stimuli, and increased vigilance for angry and happy

stimuli (Mogg, Bradley, De Bono, & Painter, 1997; Williams, Mathews, & McLeod, 1996). This latter response would serve to direct attention away from the fearful stimuli, attenuating the threat value of the stimulus, and thereby reducing anxiety. Furthermore, conscious control appears to be more likely in non-clinical, high anxiety, populations compared to clinically anxious individuals (Williams et al., 1996). Thus clinically anxious individuals show similar response bias in both subliminal and supraliminal tasks.

The *Object Relocation Task* (Kessels, Postma, & de Haan, 1999) has been proposed as a viable alternative to tasks that utilize subliminal stimuli. Specifically, this task has been found to overcome the problem of conscious control on task performance (Putman et al., 2007; van Honk et al., 2003). The task consists of sets of eight faces on a grid or blank background, displayed on a computer monitor. The sets contain four neutral faces each along with four emotional faces (i.e., faces showing emotional expressions of happiness, fear, anger, etc.). After viewing the faces, the display is emptied, and the faces reappear above the display grid / background in random order. Participants then have to move the faces using a computer mouse to their original positions on the screen. The task thus assesses spatial memory, because participants have to remember where in the computerized space the faces were originally. In light of their findings, Van Honk et al. (2003) suggest, following the motivational direction hypothesis, that because individuals high in anxiety possess a processing bias that would lead them to avoid angry and happy faces, it is likely that their spatial memory performance for these faces would be impaired. Hence, the task produces similar results to what would be expected from subliminal tasks (Putman et al., 2007; van Honk et al., 2003; van Honk & Schutter, 2006), namely, elevated levels of stress or anxiety are associated with bias towards fearful/avoidance-related stimuli and avoidance of approach-related stimuli (i.e., happy and angry faces). Evidence therefore suggests the Object Relocation Task for emotional faces is effective in overcoming the problems of conscious control in information processing observed in non-clinical high anxiety individuals.

Studies using the object relocation task to study emotional processing bias have produced results that are fairly consistent with the trends suggested by the motivational direction hypothesis. In a study using basal levels of salivary cortisol as indices of stress and low mood and measuring performance on the object relocation task (presenting only happy, angry and neutral faces), van Honk et al. (2003) found that increased levels of cortisol were significantly positively associated with increased avoidance of happy facial expressions. They also found a

similar relationship for angry faces, although this trend only neared statistical significance. In another study using the object relocation paradigm, van Honk and Schutter (2006) found that processing of anger was significantly reduced after repeated transcranial magnetic stimulation (rTMS) deactivation of the left PFC, supporting the hypothesis that left PFC would decrease the processing of anger relative to deactivation of the right PFC by rTMS.

The motivational direction hypothesis bears almost identical features to Gray's BIS/BAS model of personality. Most notably, both differentiate individual traits along an approach-avoidance dichotomy. The conceptual congruence between the theories was supported by a study examining their relationship using a subliminal/supraliminal emotional Stroop task. The authors found performance on the BAS items of the scale predicted response vigilance to angry faces, while measures of social anxiety significantly predicted avoidance of angry faces. BIS was found to correlate negatively with bias for angry faces in both the subliminal and supraliminal exposure conditions however the authors could not confirm the significance of these results (Putman, Hermanus, & van Honk, 2004).

Because adults with a history of childhood trauma are regularly found to be high in neuroticism and have been found to be at risk for higher BIS, they are likely to demonstrate information-processing bias towards fear-provoking stimuli. In a recent study examining emotional Stroop performance in psychosomatic inpatients, Wingenfeld et al. (2011) showed that a history of childhood trauma was the best predictor of mean reaction time in all three word types used in the Stroop task. The authors only state that the words were neutral, negative, and symptom-related, but provide no specific indication of what the words were. These results suggest some evidence for an emotional-processing bias in individuals with a history of childhood trauma. However, some caution is warranted. The study used the Stroop color naming task, and previous research has noted that some degree of conscious control is possible with this task; hence, results may not be an accurate reflection of actual response bias. In addition, the authors did not specify or give any indication of what the motivational direction of the negative stimulus words were (i.e., anger/approach or fear/avoidance).

In summary, the preceding discussion argued that traumatic experiences in childhood predisposes the maturing brain to alterations that are associated with increased risk of developing maladaptive personality traits in adult life. These traits signify enhanced responsiveness to stressors because of increased levels of anxiety and neuroticism within the adult survivor of

childhood trauma. Furthermore, anxiety and neuroticism appear to be associated with increased BIS activation, which is also observed in adults with a history of early adversity. Finally, BIS sensitivity appears to influence the way in which emotional information is processed and in childhood trauma victims, in line with the motivational direction hypothesis, this bias appears to favor fear-provoking avoidance stimuli.

The current study investigates whether increased BIS sensitivity will be observed in a sample of adults who have suffered traumatic childhoods and whether those adults will demonstrate similar information processing biases as those outlined in the literature reviewed above. A final objective of the current study is to establish whether it is possible to alleviate information processing bias for fear-provoking stimuli in the Trauma sample by administering the mu-opioid agonist buprenorphine during an Object Relocation Task. In order to understand why this effect may be expected the following part of the introduction will outline the neurophysiology of the stress response, which will introduce key brain regions and neurochemical processes that are implicated in mu-opioid activity. Research into the stress response has largely focused on PTSD and its associated symptoms. However, since childhood trauma does not always result in PTSD, findings related to PTSD should tentatively be extended to neurodevelopment following childhood trauma.

Neurophysiology of the Stress Response

According to the DSM-IV-TR (APA, 2000), PTSD consists of three primary symptom clusters: re-experiencing the trauma, avoidance of trauma-related external and internal cues, and hyperarousal/hypervigilance. Neurobiological models suggest that these three groups of symptoms result from prolonged physiological reactivity to traumatic stress that causes the physiological stress system to be overwhelmed (see, e.g., Weber & Reynolds, 2004). Specifically, these models suggest that an aversive stimulus causes hyperarousal of the stress system, leading to the flooding of the particular brain regions by the neurochemical constituents that help activate and regulate this system's various responses. The result is dysregulation and structural alteration within the various brain regions associated with managing reactions to stress. These regions include the PFC, the amygdala, the hippocampus, the dorsal raphe nucleus, and the locus coeruleus. Three neurotransmitter / neurohormone systems have also been identified as playing an important role in mediating the stress responses: (a) the noradrenergic system, (b) the

serotonergic system, and the (c) hypothalamic-pituitary-adrenal (HPA) axis (Vasterling & Brewin, 2005).

The locus coeruleus (LC) contains the majority of the brain's noradrenergic cell bodies (Zigmond, Finlay, & Sved, 1995). When activated, these nuclei trigger a state of arousal in the organism, directing attention, increasing vigilance and alertness, and mediating cardiovascular responses to threat-provoking stimuli (Aston-Jones, Raikowski, Kubiak, & Alexinsky, 1994). Diverse afferent inputs in noradrenergic neurons facilitate the processing of relevant sensory information, while its large efferent network facilitates anxiety and fear-related skeletomotor, cardiovascular, neuroendocrine, and cognitive responses. Stimulation of the LC manifests in fear-related behavioural responses and increased NE release throughout the brain in regions such as the amygdala, hippocampus, hypothalamus, and PFC. These brain regions are associated with the perception, evaluation, remembering, and response to fear-inducing stimuli (Zigmond et al., 1995). In states of extreme arousal, such as when confronted with severe stress, these regions are overwhelmed with NE, leading to impairment of their functioning (Arnsten, 2000; Birnbaum, Gobeske, Auerbach, Taylor, & Arnsten, 1999).

After the organism is exposed to a stressor, the PFC (and, in particular, the orbitofrontal cortex), amygdala, and the hippocampus are further subjected to the effects of serotonin, which is released by the serotonergic system in response to that stressor. The serotonergic system is mediated by the raphe nuclei of the brainstem, which contain the majority of cell bodies responsible for the release of serotonin (Bremner et al., 2003; Nestler, Hyman, & Malenka, 2001; Koenen et al., 2001).

Glucocorticoids are another important neuromodulator in the physiological stress response. Their release is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is a closed-loop system that activates and inhibits its own response. Under conditions of traumatic stress, the system's regulatory mechanism fails to inhibit the production of glucocorticoids, causing an excess amount to be released into the brain (Bowman, 2005). Specifically, the HPA axis is a closed-loop neurocircuit controlled by a regulatory set of afferents, mostly the neurons in the paraventricular region of the hypothalamus. When the brain recognizes a stressful event or stimulus, these neurons secrete corticotrophin-releasing hormone (CRF). CRF stimulates the anterior pituitary gland to release adrenocorticotrophic hormone (ACTH), which then stimulates the adrenal gland to secrete glucocorticoids. The secretion of

glucocorticoids regulates the entire HPA axis by providing negative feedback to stop further CRF and ACTH release (Bowman, 2005). Increasing levels of glucocorticoids have been shown to disrupt the functioning of the PFC (Roozendaal, McReynolds, & McGaugh, 2004) and the hippocampus (Het, Ramlow, & Wolf, 2005; Kim & Diamond, 2002).

These findings demonstrate the complexity of the mammalian stress response: a system of interconnected brain structures (e.g., PFC, amygdala, LC, dorsal raphe nuclei, HPA axis, etc.) that communicate via specific hormones and monoamines / indolamines (e.g., NE, serotonin, GC, etc.) in response to threatening stimuli. The system increases the state of arousal and prepares the individual to react behaviourally and cognitively to stressors. However, intense/ repetitive / prolonged activation of this system may cause neurobiological alterations in the brain structures that mediate the stress response. These structures are outlined below, and represent important components of the pathological stress response observed in individuals with elevated levels of anxiety such as in adults with a history of childhood trauma. Furthermore, these structures represent the neuroanatomical components upon which the mu-opioid agonist buprenorphine exerts its unique pharmacological properties (described later).

Neurological correlates of pathological stress responses. Prolonged hyperarousal leads to damage of brain regions responsible for the stress response that may lead to dysregulation of stress responsivity, which in turn is associated with elevated levels of anxiety (Perry et al., 1995; Teicher et al., 2003; Weber & Reynolds, 2004). As noted above, these regions include the PFC, amygdala, and the hippocampus. For the purposes of this study, the focus will be mainly on the PFC and the amygdala, for the following reasons: The PFC has an inverse relationship with the amygdala, providing an inhibitory function to the negative affective responses of the amygdala (Kim & Diamond, 2002). In individuals who have experienced traumatic stressors, this action is reversed, allowing the amygdala to create a state of fear-induced hyperarousal (Liberzon et al., 2002). In addition, these structures bare further relevance to this study since it appears that mu-opioids may reduce response bias associated with elevated anxiety through its actions within the PFC and amygdala (Panksepp, 2003).

Prefrontal cortex. Glucocorticoids and catecholamines have been found to optimize the functioning in the amygdala, but they have an opposite effect on the PFC, impairing the functioning of this brain region (Southwick et al., 2005). Optimal functioning of the PFC is critical to success on cognitive tasks such as planning, guiding, and organizing behaviour

(Goldman-Rakic, 1987). Furthermore, moderate levels of catecholamines are vital to the working memory function of the PFC, but high levels of catecholamines and glucocorticoids are associated with impaired functioning in this region (Arnsten, 2000). It is therefore notable that exposure to even mild stressors brings about high levels of catecholamine release in the PFC (Goldstein, Rasmussan, Bunney, & Roth, 1996).

The excessive release of NE under conditions of severe stress creates a chemical context that suppresses the functions of the PFC. The functional effects of NE on PFC are mediated by postsynaptic $alpha_1$, $beta_1$, and $alpha_{2A}$ receptors. Specifically, at moderate levels NE binds with $alpha_{2A}$ receptors, which improve PFC functioning, thus acting as a protecting agent. However, high levels of NE under high stress conditions, activates $alpha_1$ receptors, thus causing PFC dysfunction (Southwick et al., 2005). Interestingly, it appears that individuals with PTSD have reduced levels of $alpha_2$-adrenergic receptor numbers compared to healthy controls, as well as more NE excretion as measured over a 24-hour period (Perry, 1994).

Taken together, through the actions of NE, severe stress creates a depressed environment within the PFC, while at the same time stimulating amygdala activity. The implications of a hypoactive PFC together with a hyperactive amygdala are addressed below. For the moment, however, we focus on the fact that NE is not the only catecholamine acting on the PFC.

It appears that the negative effects of catecholamines and glucocorticoids on the working memory function of the PFC can be reproduced by dopamine D_1 agonist infusion into the PFC and inhibited by dopamine D_1 receptor blockade (Southwick et al., 2005). Dopamine (DA) is an important stress neuromodulator. Following exposure to extreme stress, the resultant release of DA in the PFC overstimulates this region, leading to reduced responsiveness, and thereby diminishing the functioning of the PFC. The resulting dysfunction in the PFC is associated with the symptoms of hypervigilance and paranoia in PTSD (Weber & Reynolds, 2004). The pathology underlying the PFC is also related to the intrusive symptoms experienced in PTSD. Hypoactivation of the PFC leads to an inability to suppress involuntary thoughts and direct attention, presumably leading to intrusive symptoms (Kanagaratnam & Abjormsen, 2007).

Importantly, Teicher et al. (2003) state that the PFC may be especially vulnerable to the effects of trauma in childhood. The authors believe the vulnerability of the young PFC to traumatic stressors stem from this regions' relatively high density of glucocorticoid receptors coupled with its delayed ontogeny.

As mentioned above, the effects of severe stressors subject the PFC to a state of hypoactivity. This is a significant component of the exaggerated stress response seen in individuals with heightened levels of anxiety as the PFC is thought to play an inhibitory role on fearful responses (Liberzon et al., 2002). An additional component to the hypersensitive stress response in high anxiety individuals is the anterior cingulate cortex (ACC) found within the medial prefrontal cortex (mPFC). The ACC is associated with the generation of the affective experience of pain. Findings show that activation of this region is positively associated with feelings of social distress and self-induced sadness (Eisenberger, Lieberman, & Williams, 2003; Mayberg, 1997). Trauma related alterations in this region are associated with decreased inhibition of ACC-induced emotional reactivity (Liberzon, et al., 2007).

Amygdala. The amygdala is a brain region crucially involved in both the detection and expression of fear (Davis, 1992). It is connected to the hypothalamus and brainstem nuclei that mediate fear responses, including freezing behaviours, alterations in heart rate and blood pressure, sweat gland activity, and release of stress hormones. Catecholamines play a key role in the amygdala, enabling encoding, consolidation and retrieval of memory for events and stimuli that are arousing, stressful, and fear provoking (Southwick et al., 2005).

Optimal functioning of the amygdala occurs during stress exposure. This is because, during such exposure, the neurochemical environment within the amygdala consists mainly of high levels of catecholamines and glucocorticoids, which assists in the consolidation of emotionally relevant memories and in fear conditioning (Southwick et al., 2005).

Increased levels of NE are observed in chronically stressed organisms. Subsequent arousal would then exaggerate the levels of NE and glucocorticoids in the amygdala and PFC. While this would create an optimal environment in the amygdala, high levels of NE in the human PFC would likely impair executive functioning, giving greater control to the amygdala to govern behaviour and physiological reaction. The result of this sequence of events would be increased fear-related behaviour (Davis, 1992), such as an exaggerated startle response, increased fear conditioning, increased vigilance, insomnia, impulsivity, and so on.

Greater left amygdala responses to traumatic versus neutral cues have been observed in PTSD subjects compared to controls, while it appears that symptom severity can be correlated with regional cerebral blood flow (rCBF; indicating increased metabolic activity) within the right amygdala in PTSD groups (Shin et al., 2004). rCBF also appears to correlate positively with self-

reported anxiety in PTSD participants (Pissiota et al., 2002). Etkin and Wager (2007) conducted a meta-analysis of imaging studies examining functional neurobiological deficits in PTSD, social anxiety disorder, and specific phobias and found that hyperactivity of the amygdala was a consistent symptom across all three disorders.

The experience of childhood has also been suggested to induce similar alterations in the activity of the amygdala. Specifically, neurodevelopmental changes in the amygdala subsequent to the experience of a traumatic event are associated with decreases in inhibition of amygdala activation, resulting in elevated fearfulness and anxiety in later life (Teicher et al., 2002, 2003).

In summary, studies investigating the structure and functioning of brain pathology associated with PTSD and other anxiety disorders have found varying degrees of abnormalities/deficiencies in the amygdala and the PFC. The evidence suggests that in individuals with elevated anxiety, the amygdala displays heightened activation, while the PFC displays an opposite tendency to decrease in activation; hence, one observes an inverse relationship between the amygdala and the PFC. This pattern of activation between the amygdala and the PFC helps explain the increased incidence of anxiety and neuroticism in adults who have suffered childhood adversity. Panksepp (2003) hypothesizes that the experience of negative affective states such as fear may be alleviated by the administration of exogenous mu-opioid agonists. If this assertion is correct, the administration of exogenous mu-opioid agonists to high anxiety individuals may result in decreased negative affect and, by extension, decrease the fear response in this population possibly leading to the attenuation of avoidance related response bias. The possible mechanisms underlying this process are discussed below.

mu-Opioids

The mu-opioid system comprises three classes of endogenous opioid peptides: endorphins, enkephalins, and dynorphins. These opioids bind with three families of opioid receptor: mu, kappa, and delta. Mu-opioid receptors are responsible for the regulation of brain regions and neurotransmitter systems that mediate the processing of emotional information, stress responses, and reward (Mansour, Fox, Akil, & Watson, 1995). These regions include, the ACC, PFC, insular cortex (IC), amygdala, thalamus, and basal ganglia (Firestone et al, 1996; Schlaepfer et al., 1998; Wagner et al., 2001; Zubieta et al., 2003).

mu-Opioids have been found to have analgesic effects, through inhibiting pain induced neuronal activity (Casey et al., 2000). Pain relief is associated with increased concentrations of mu-opioid receptors in regions including ACC, IC, PFC, thalamus, and basal ganglia (Apkarian et al., 2005; Jones et al., 1999). Furthermore, Zubieta et al. (2001) found reductions in mu-opioid receptor availability in the ACC, PFC, IC, thalamus, ventral basal ganglia, amygdala, and periaqueductal grey were observed in patients with sustained muscular pain. Reductions in mu-opioid receptor availability suggests decreased activation of this neurotransmitter system in the relative brain regions. The authors also found a correlation between the mu-opioid neurotransmitter system and the suppression of sensory and affective qualities of pain. These findings indicate that the analgesic properties of mu-opioids work through very similar brain systems as those altered through the experience of traumatic stressors (i.e., PFC, ACC, amygdala). In addition, the analgesic properties of mu-opioids involve both the suppression of physical pain and the affective component of pain.

The opioid system is essential in the activation of pleasurable, and the inhibition of negative, emotional states (Nelson & Panksepp, 1998; Panksepp, 2003). As mentioned earlier, mu-opioid receptors are concentrated in the ACC. Increased activation of this region is associated with both psychological pain and the experience of social distress. mu-Opioid neurotransmission in this region is associated with inhibition of this kind of negative emotional reactivity (Liberzon et al., 2007). Furthermore, greater levels of activity in the ACC are associated with decreased activity of the PFC, and visa versa, suggesting an inhibitory role of the PFC on the ACC (Panksepp, 2003).

Liberzon et al. (2002) found that increased mu-opioid availability in three areas of the amygdala was associated with a reduction in the neural intensity of emotional response to aversive emotional pictorial stimuli (e.g., mutilated faces, dead bodies, etc.). The authors found a negative correlation between rCBF in these regions and mu-opioid availability at baseline. These observations suggest an inhibitory role of the mu-opioid system in response to aversive stimuli in the amygdala. These authors also found a negative correlation in rCBF between the mPFC and the left amygdala, suggesting a possible inhibitory role of the PFC on amygdala activation. Furthermore, Liberzon et al. (2007) assessed two groups of combat veterans (PTSD and non-PTSD with combat exposure) and a matched control group (without prior trauma exposure). In both the trauma-exposed groups they found that in regions where mu-opioid activity causes

inhibition of the amygdala (rostral component of the extended amygdala) there were less mu-opioid receptors compared to those same regions in the control groups. Hence, mu-opioid agonists released in this region would have limited receptors to bind to, and consequently exert less of an effect. In the caudal amygdala on the other hand, where direct mu-opioid activity increases activation of the amygdala, there was no decrease of receptors in the PTSD group, leaving them vulnerable to enhanced amygdala activity and a focus on negative emotion (Liberzon et al., 2007).

In summary, mu-opioids are concentrated in similar brain regions as those which are involved in the stress response (e.g., PFC, ACC, amygdala, etc.). Within these regions mu-opioids are responsible for the inhibition of negative affective responses. Decreases of mu-opioid receptor availability within the ACC are associated with increased social distress, while similar mu-opioid dysregulation within the amygdala is associated with an increased fear response. These abnormalities in ACC and amygdala mu-opioid receptor availability have been observed in victims of trauma and possibly contribute to the elevated levels of anxiety and hypersensitive stress response observed in this population of individuals. Finally, a lack of mu-opioid mediated inhibition of the ACC and the amygdala is associated with decreased PFC activation. Abnormalities in mu-opioid mediated neurotransmission in victims of trauma may therefore contribute to the hyperactivation of the amygdala and hypoactivation of the PFC observed in this population.

Given the findings by Liberzon et al. (2007), reduced mu-opioid regulation may also be observed for adults with a history of childhood trauma. Administration of exogenous mu-opioid agonists, as happened in this study, could compensate for the shortage of mu-opioid mediated neurotransmission inducing anxiolytic effects within trauma-exposed individuals. The present study examines these effects in relation to performance on an Object Relocation task for emotional faces. It is hypothesised here that administration of an exogenous mu-opioid agonist will have the effect of reducing avoidance-related response bias in adults with a history of childhood trauma.

mu-Opioid agonist buprenorphine. Buprenorphine is the mu-opioid agonist used in the present study. It has high affinity (i.e., strong interaction with receptors) for mu-opioid receptors and full agonistic (i.e., its analgesic effects are dose dependent, exhibits no ceiling effects, and can reach 100% occupancy at receptors) properties at these receptor sites (Ding & Zaffa, 2009;

Pergolizzi et al., 2010; Raffa & Ding, 2007).While buprenorphine has no ceiling effect with regard to its analgesic properties, there is a ceiling effect for respiratory depression (unlike other mu-opioid full agonists, e.g., morphine), which reduces the likelihood of this potentially fatal event from occurring and therefore contributing to its' safety in clinical use. In addition, buprenorphine is considered safe to use in combination with other opioids (e.g., morphine), and is considered a safe and effective option for the treatment of chronic pain conditions (Pergolizzi et al., 2010).

Conclusion

Childhood trauma has been associated with increased vulnerability for the development of a psychiatric disorder in later life including a range of personality disorders. Neuroticism and heightened BIS activation are examples of personality traits that are associated with adult survivors of childhood trauma. These traits are related with elevated levels of anxiety in this population. Increased anxiety predisposes the victim to a response bias for fear-related stimuli, and avoidance of approach-related stimuli. Furthermore, it may be possible to attenuate that bias through the administration of exogenous mu-opioids. mu-Opioids exert their effects on similar brain regions as those that mediate the stress response, and since adults with a history of early adversity have possibly been subjected to extreme stressors in childhood, those regions may be particularly susceptible to the effects of the drug.

Specific Objectives of the Current Study

The neurobiological consequences that occur after experiencing a traumatic event, whether in childhood or later in adult life, are complex and multi-faceted. The experience of severe stress results in a range of neurophysiological changes that predisposes the victim to a host of behavioural, cognitive, and emotional distortions that may lead to disorder. These changes have only recently been investigated in those with a history of early adversity, including childhood trauma. The aim of this study was to contribute to the existing literature describing the relationship between adverse childhood experience and adult personality traits, and associated bias in information processing. A further contribution of the current study involves measuring the possible attenuating effects of mu-opioid agonist buprenorphine on the information-processing bias observed in individuals with elevated levels of anxiety.

Trauma status in the current study was determined by participants' self-reports on the Childhood Trauma Questionnaire – Short Form (CTQ-SF; Bernstein et al., 2003). Specifically, those individuals who obtained a score in the moderate to severe range on at least one CTQ-SF subscale constituted the Trauma group. Individuals with either (a) scores in the minimal range on all CTQ-SF subscales, or (b) a score in the low to moderate range on only one CTQ-SF subscale constituted the Control group. The design of the study allowed, as a preliminary step, investigation of the psychometric properties of the CTQ-SF. Specifically, the test-retest reliability of the CTQ-SF was examined over three separate administrations, spanning at least 1 week between the first and second administrations, and at least 1 week between the second and third administrations.

Following this preliminary step, I tested the following specific hypotheses, all of which emerged from the literature reviewed above:

1. With regard to BIS/BAS sensitivity, adults who have experienced childhood trauma will have heightened BIS activation, given increased levels of anxiety and neuroticism observed in this population, compared to healthy matched controls. Increased BIS activity will be reflected in higher scores on the BIS index of the BIS/BAS scale (Carver & White, 1994). I predicted that there would be no significant differences between the Trauma and Control groups in terms of BAS sensitivity because elevated levels of anxiety, such as those associated with a history of childhood trauma, are not related to BAS activation.
2. On the Object Relocation Task, adults with a history of childhood trauma will demonstrate an information-processing bias for threat-related stimuli and avoidance of approach-related stimuli. These biases will be reflected by smaller error scores, compared to healthy matched controls, in the relocation of fearful faces to their original locations, and larger error scores, compared to the same controls, in the relocation of angry and happy faces to their original locations.
3. Attenuating effects of buprenorphine on performance for the fearful faces condition will be observed for the Trauma group, but not the controls. Thus, error scores of the Trauma group for threat-related stimuli will increase subsequent to buprenorphine administration, yielding significant within-group differences for the Trauma participants on their performance between the medication and placebo conditions.

METHODS

Participants recruited into this study were part of a larger research programme examining the effects of buprenorphine on affective experience, social behaviour, and neural circuits in individuals with and without a history of childhood trauma. Potential participants underwent rigorous screening procedures that were part of multiple phases of data collection. These phases consisted of the following: First, an initial online questionnaire attracted a large number of potential participants (N = 856). This screening survey was followed by an in-person screening interview and testing session, which helped narrow down the list of potential participants until it was possible to have two clearly defined sample groups, namely, a Trauma and a Non-Trauma (i.e., control) group. Once these groups were established participants within each group underwent two phases of testing (Behavioural 1 and Behavioural 2), during which multiple questionnaires were delivered and various neuropsychological tests administered. The mu-opioid buprenorphine was administered to each participant during only one of these sessions, while in the other session participants received a placebo. Participants were not informed about whether they had received the drug or the placebo. In addition, the researchers involved in data collection were blind to the medication condition. The final phases of the larger research project consisted of two neuroimaging sessions, one under medication and one under placebo, where participants underwent fMRI scanning to investigate possible functional effects of buprenorphine. The phases/sessions relevant to the current study, and the measurement instruments associated with each, are outlined below.

Participants and Procedure

Online screening phase. A total of 856 adults between the ages of 18 and 28, primarily from the University of Cape Town's student population and surrounding community, were recruited into the larger study of childhood trauma and its consequences. Posters advertising the research were placed in and around most departments on campus, as well as in student residences and on public notice boards. The posters directed interested individuals to an online survey that acted as the initial screening procedure.

Individuals who completed the survey were excluded from further participation in the research reported here if their self-rating on the Edinburgh Handedness Scale (Oldfield, 1971) suggested that they were primarily left-handed. Only right-handed participants were included in the

study in order to eliminate the possibility of individual differences in cerebral functional organization. Thirty-nine individuals who completed the survey were excluded from further participation on this basis.

Additionally, individuals who completed the survey were excluded from further participation if they reported on the List of Threatening Experiences (LTE; Brugha & Cragg, 1990) having faced a number of distressing and potentially traumatic events within the previous 6 months. This sampling criterion was put in place because the study focused only on individuals with a history of childhood trauma. Eleven individuals who completed the survey were excluded from further participation on this basis.

Individuals who completed the survey but who obtained high scores on the Minimalization/Denial subscale of the Childhood Trauma Questionnaire – Short Form (CTQ-SF; Bernstein et al., 2003; Appendix B) were excluded from further participation. This sampling criterion was put in place because the CTQ-SF was the only measure of childhood trauma used in this study, and therefore it was essential to exclude all questionable CTQ profiles. Twenty-three individuals who completed the survey were excluded from further participation on this basis.

Finally, individuals who completed the survey but who obtained a low to moderate score on two or more subscales of the CTQ-SF, and did not have at least one moderate to severe score on at least one CTQ-SF subscale, were excluded from further participation. Six hundred and seventy individuals who completed the survey were excluded from further participation on this basis. This latter sampling criterion was put in place to help ensure that we could establish two clearly defined groups:

1. A Control group, consisting of individuals with either (a) scores in the minimal range on all CTQ-SF subscales, or (b) a score in the low to moderate range on only one CTQ-SF subscale. After application of the screening criteria described above, this group consisted of 68 participants.
2. A Trauma group, consisting of individuals with a score in the moderate to severe range on at least one CTQ-SF subscale. After application of the screening criteria described above, this group consisted of 45 participants.

In summary, after analyzing the data derived from the online survey, 113 of the 856 individuals who had completed the survey were deemed eligible to continue participation in the research reported here. These individuals were contacted telephonically for additional screening. At this stage of the study, 4 individuals either declined to participate further[1] or were unreachable.

Telephonic screening phase. The remaining 109 individuals were contacted via telephone in order to conduct a clinical interview that screened for the presence of the following: a history of substance abuse; a history of any DSM Axis I psychiatric disorder or Axis II personality disorder; a history of neurological disease; and current psychoactive prescription medication. The presence of any one of these led to the individual's exclusion from further participation. The reasons these exclusion criteria were set in place include the fact that previous studies have shown that some prescription medications (e.g., selective serotonin reuptake inhibitors), excessive substance abuse, and comorbid psychiatric disorders may influence brain size and functionality (Jatzko et al., 2006; Smith, 2005). The clinical interview led to the exclusion of 31 individuals from further participation. Nine participants met the diagnostic criteria for depression, three for dysthymia, 12 for alcohol and substance abuse, and seven for panic disorder, general anxiety disorder, and social phobia. After telephonic screening, nine more individuals chose to withdraw from the study.[2] The remaining 69 individuals were invited for an in-person interview and testing session.

The in-person interview and testing session. This interview and testing session was conducted in the Applied Cognitive Science and Experimental Neuropsychology Team (ACSENT) laboratory in the UCT Department of Psychology. The participants were asked to fill out another CTQ-SF, as well as a BIS/BAS questionnaire (Behavioural Inhibition System / Behavioural Activation System; Carver & White, 1994; Appendix C). Those with CTQ-SF scores (see Appendix A) that were inconsistent across the online and in-person administrations were excluded from further participation, i.e., if their trauma classification differed on the two administrations, or if either were rated as of questionable validity, using the validity items built into the CTQ-SF, then those participants were not included. Furthermore, one of the scores per

[1]These participants declined due to personal reasons, including work and course commitments.

[2]These individuals declined further participation due to personal reasons, including work and course commitments.

person could be rated as displaying "some minimization/denial", though if both ratings did, then this was grounds for exclusion as well. On this basis, we excluded 25 participants (16 from the Control group and nine from the Trauma group).

The BIS/BAS questionnaire was initially scheduled to be administered only during the first scan of the scanning phase of the larger research project. However, we subsequently administered the BIS/BAS at either the in-person interview or during the Behavioural 1 session because of time constraints during the scanning sessions.

The behavioural testing sessions. At this point, 44 participants continued to undergo behavioural testing, which occurred over two sessions. The two behavioural sessions for each participant were scheduled with at least a 1-week interval inbetween. Mu-opioid agonist buprenorphine and placebo was administered in alternating sessions for each participant. Experimenters and participants were blind as to the drug schedule. Administration of the placebo and mu-opioid agonist buprenorphine occurred at the start of the session. Based on previous literature, we estimated that the drug would exert its' strongest effect after approximately 90 minutes (e.g., Walsh, Preston, Stitzer, Cone, & Bigelow, 1994). During that interval, participants were assessed on a range of tasks that were not related to the intervention of the drug. The BIS/BAS scales were administered during the first behavioral testing session within the 90 minutes before the drug was digested. The object relocation task was administered within both behavioural sessions after the 90 minutes had elapsed. Once the 44 participants concluded behavioural testing, they continued into the fMRI stage of the larger research project.

The scanning phase. In summary, then, 44 participants (20 who had experienced at least one moderate to severe childhood trauma but who did not carry a diagnosis of current PTSD, and 24 healthy controls) remained eligible for the scanning phase of the larger study. Before either of the scans, participants completed their final CTQ-SF and BIS/BAS questionnaires. The BIS-BAS scales were administered during the testing phase of the first scan, while the CTQ-SF was administered during the testing phase of the second scan. The questionnaires were completed within 90 minutes after administration of either the placebo or buprenorphine (i.e., within the threshold before buprenorphine was to take effect). This procedure was followed in order to avoid any effect of the drug on completion of the questionnaire.

To conclude, data from 38 participants were used in the analysis of the Object Relocation Task. Of those participants, BIS/BAS data were available for 36 participants, while 29 completed

all three CTQ-SF questionnaires (i.e., administered in the online survey, at the in-person interview, and at the second scanning session).

Materials and Medication

Buprenorphine. Participants in both the control and trauma groups were administered 0.2 mg of the mu-opioid agonist buprenorphine and placebo (sublingual) in alternating sessions within both the behavioural and scanning parts of the study. The experimenters and participants were blind to the schedule of the drug. In addition, the medications were consumed at least 90 minutes before commencement of the object relocation task, to ensure an optimal effect of the drug.

Object Relocation Task. This is a computerized task that assessed memory for emotionally-laden faces presented on a screen. Participants received one practice trial each after which the actual task began and their performance was measured. Eight faces appeared on a screen, of which four were neutral faces and four were in either a state of anger, fear, or happiness. Only one emotion was on display within each trial. There were 12 trails in total (four trials for each of the three emotions).

On each trial, the stimuli were presented on a gray background. After 30 s, this background was emptied, and the faces re-appeared above it in random order. The participant then had to move the faces to their original positions on the background using a computer mouse.

The outcome variable here is deviation (in millimetres) between the participant's indicated position for each face and its original position. Indices for memory/attentional bias were derived by subtracting performance on the angry/happy/fearful faces from performance on the neutral faces (similar analyses are described by Van Honk & Shutter, 2006). Figure 1 represents a screen shot from the Object Relocation Task (neutral faces condition) used in the present study.

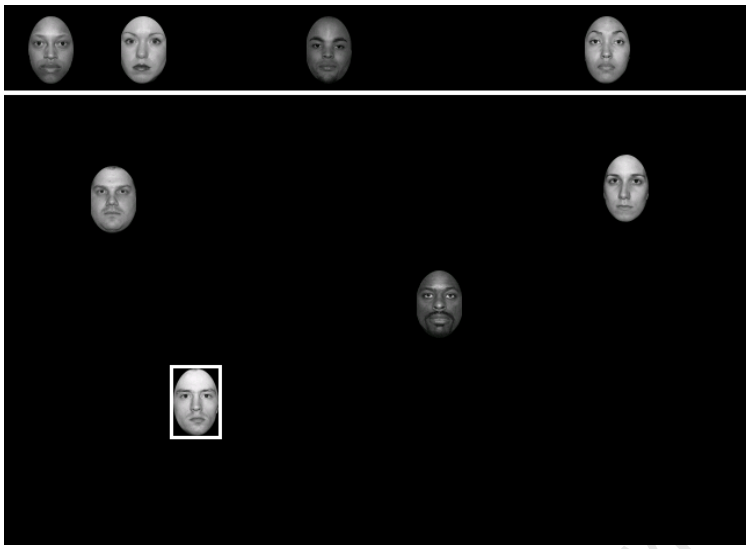

Figure 1. Screen shot of the Object Relocation Task in the neutral faces condition

Childhood Trauma Questionnaire – Short Form (CTQ-SF). The CTQ-SF (Bernstein et al., 2003) is a retrospective self-administered instrument that was developed and validated as a rapid assessment screening tool for maltreatment histories in both clinical and non-clinical individuals. The CTQ-SF is a 28-item version of the original 70-item Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998; Bernstein et al., 1994), which also assesses early adversity. It contains five subscales, three assessing abuse (Emotional Abuse, Physical Abuse, and Sexual Abuse) and two assessing neglect (Emotional Neglect and Physical Neglect). Respondents are required to rate the extent to which they experienced different traumatic childhood events. Each subscale contains 5 question items; responses are recorded on a 5-point Likert-type scale, ranging from "never true" to "very often true". The minimum score of 5 on a particular subscale indicates no history of abuse or neglect, while the maximum score of 25 indicates an extreme history of abuse or neglect. The instrument also contains a three-item Minimization-Denial subscale to help detect false-negative trauma reports.

The CTQ-SF has demonstrated good criterion-related validity when compared to therapists' ratings of a group of psychiatrically referred patients, on whom corroborative data were available (Bernstein et al., 2003). Although the original CTQ showed excellent test-retest reliability over a 2-to 6-month interval (Bernstein et al., 1994), there are currently no data available for the test-retest reliability of the CTQ-SF. Filling this gap in the literature constitutes a major component of the current study.

The CTQ-SF was suitable for the purpose of the current study as it is brief (it can be administered in only 5 minutes) and appropriate for use in the target population (Raudsepp, 2006). The CTQ-SF has successfully been used to investigate childhood trauma in the South African context (Lochner et al., 2004).

Edinburgh Handedness Inventory. This instrument is a self-report measure of hand preference (Oldfield, 1971). The respondent is required to indicate which hand he/she would be most likely to use to complete 10 common household or sport-related actions that require the use of one hand to complete (e.g., brushing ones teeth, or writing). This instrument has high internal consistency and has been shown to be useful for screening purposes, especially where large populations are involved and where a standard of comparison in neuropsychological work is needed. It is also a reliable screening tool in populations that differ across gender, socio-economic, and cultural lines (Oldfield, 1971; Williams, 1991).

List of Threatening Experiences (LTE). The LTE (Brugha & Cragg, 1990) is a self-report measure designed to identify the presence of stressful life experiences. The 12 items on the instrument relate to events such as serious illness, death of close friends or family members, and major financial crises. Respondents are required to highlight whether they have experienced any of these events either in the past 6 months or more than 6 months ago. The LTE was chosen because it is relatively quick to administer, requiring only 5-10 minutes to complete. It has also demonstrated good test-retest reliability and concurrent validity (Humke & Radnitz, 2005). This instrument has proven useful in the assessment of traumatic events in South African populations (Seedat et al., 2004).

Behavioral Inhibition System/Behavioral Approach System (BIS/BAS) Scales. The BIS/BAS (Carver & White, 1994) is a self-report scale that measures sensitivity in the activation of two general motivational systems that are theorized to underlie behavior and affect: a behavioral inhibition system (BIS) and a behavioral approach/activation system (BAS). The scales consist of 20 question items scored on 4-point Likert scales. The BIS scale includes 7 items that assess sensitivity to external cues of punishment, fear, and anxiety-provoking events (e.g., “I feel worried when I think I have done poorly at something”). The BAS scale includes 13 items, which are divided across three subscales. The subscales are Drive (4 items, e.g., “I go out of my way to get things I want”), Fun Seeking (4 items, e.g., “I crave excitement and new sensations”), and Reward Responsiveness (5 items, e.g., “When I get something I want, I feel

excited and energized"). Higher scores on each of the items indicate greater sensitivity of the system being measured. The BIS/BAS scales have demonstrated good test-retest reliability, internal consistency and a valid factor structure (Carver & White, 1994; Jorm et al., 1999).

Ethical Considerations

Ethical permission for the study was granted by the Research Ethics Committee of the University of Cape Town (UCT) Faculty of Health Sciences, by the Research Ethics Committee of the UCT Department of Psychology, and by the Stellenbosch committee for clinical trials register.

Participants received monetary compensation at the end of the first and second scan. Upon conclusion of their involvement in the study (i.e., after the second scan) participants were also provided with a compact disc containing 3 dimensional fMRI images of their brains. Consent forms (see Appendix D, E, F) were provided to and signed by all participants in the study. These forms guaranteed confidentiality and provided details of the study and ensured the safety of the medication to be administered. The information provided in the consent forms contained no specific aims of the study, to avoid bias in performance that such information may produce. The experimenters involved in the study were trained on administration of relevant questionnaires and procedures for drug administration.

Data Analysis: Scoring procedures

To fully understand the nature of the outcome variables presented in the analyses, descriptions of the scoring procedures for the three measures used in this study are described below.

CTQ-SF and BIS/BAS scales. Similar procedures were used to score both of these questionnaires. Both scales consist of various subscales. Scores on each of the question items for these subscales were added together to produce, first, a score for that subscale and, then, a total score for the entire questionnaire. For both the CTQ-SF and the BIS/BAS, higher scores on each of the subscales means a higher presence of the trait/characteristic represented in that subscale.

Conversion of scores for the object relocation task. The initial outcome of performance on the Object Relocation Task is the amount of deviation, in number of pixels, of each of the relocated faces from their original position on the computer screen to the position in which the

participant placed them. The software underlying the program produces a deviation score in pixels on both an X and Y axis of the computer monitor. Thus, for each face relocation there will initially be two scores, an "X-deviation-in-pixels" and a "Y-deviation-in-pixels". Before producing an average deviation across both axes, the pixel deviation was converted manually into millimetres for both axis results. This was done by dividing the deviation in pixels by the resolution of the screen for the given axis (X or Y, depending on which axis the deviation score that was being converted lay) and multiplying that by height or width of the monitor depending on the relevant axis (Y = height; X = width) being converted. The result is deviation in millimetres upon one axis only. The conversion thus needs to be done for both X and Y deviation-in-pixel scores. Once scores for both axes were converted to millimetres, those scores were then averaged. This resulted in an average deviation in millimetres for each relocated face. This procedure was carried out for both the emotional faces and the neutral faces, across both the medication and the placebo conditions.

Once the scores were converted, performance on the emotional faces was subtracted from performance on the neutral faces to produce an attentional bias score for each of the emotional face conditions. If the result was a negative score, that number would be converted to positive since the measure of interest was a unit of distance. This score represented the amount of error in distance the participant had produced in relocating the emotional face. Each participant received 12 scores: four scores for performance on each of the emotions presented by the faces (happy, fear, and angry). These scores were then averaged across each of the emotions to produce an average performance for each emotional face condition. The 12 scores were thus reduced to three scores for each participant (one each for happy, fear, and angry). This analysis was carried out for both the medication condition and the placebo condition, resulting in a final tally of six scores per participant.

Statistical Procedures

For all statistical analyses, descriptive statistics were explored first. This exploration allowed for an initial examination of the surface features of the variables under investigation (e.g., participant characteristics, possible group differences in performance, etc.). Examination of the descriptive statistics was also important because it allowed for the testing of assumptions that must be upheld before the relevant inferential statistics could be computed.

Between-groups comparison of demographic, clinical, and personality characteristics. In order to examine whether the Trauma and Control groups were matched according to key demographic variables, a series of one-tailed *t*-tests were conducted on all continuous variables, and a series of chi-square (χ^2) analyses were conducted on all categorical variables. A series of one-tailed independent samples *t*-tests were also computed to investigate whether the two groups in the current study were significantly different in regard to key clinical and personality characteristics (i.e., scores on the BIS/BAS and CTQ-SF subscales).

Test-retest reliability of the CTQ-SF. To explore the test-retest reliability of the CTQ-SF, Pearson's product-moment correlation coefficients (*r*) were conducted on data from the three administrations of the CTQ-SF. These correlations were computed for all the subscales individually and for the total CTQ-SF score.

Medication effects and performance on the Object Relocation Task. To investigate differences in attentional bias as measured by this task, and possible medication effects on task performance, a 2 x 6 repeated-measures factorial ANOVA was performed, taking into account the effects of multiple trials on task performance.

For all analyses, the threshold for statistical significance was set at $\alpha = 0.05$. All analyses were conducted using the software package Statistica version 9 (Statsoft, 2009). Effect size estimates were calculated and reported, where appropriate.

RESULTS

Socio-Demographic Characteristics of the Sample

As shown in Table 1, the Trauma and Control groups were well matched in terms of age and sex. There was some diversity in terms of the racial composition of the groups, however.

Table 1
Demographic Characteristics of the Current Sample (N = 38)

Outcome variable	Sample (*n* = 38)	Trauma (*n* = 16)	Control (*n* = 22)
Age (in years)	22 (4.514)	22.062 (4.781)	21.955 (4.424)
Sex (M:F)	19:19	8:8	11:11
Race			
% Black African	34	37.5	32
% White	34	18.75	45
% Coloured	24	25	23
% Asian	5	12.5	0
% Indian	3	6.25	0

Note. For all the variables not presented as percentages or ratios, means are presented with standard deviations in parentheses.

Age. In order to assess for possible between-group differences in terms of age, a two tailed *t*-test was performed on the data. Levene's test showed that the assumption of homogeneity of variance was upheld, $F(1, 36) = 0.060$, $p = 0.807$. A two-tailed *t*-test with pooled variance estimates indicated that there were no statistically significant between-group differences in terms of age, $t(36) = 0.072$, $p = 0.943$.

Sex. As shown in Table 1, there were exactly identical male to female ratios in the sample and within the Trauma and Control groups. Therefore, no additional inferential tests were necessary to confirm that there were no between-group differences in terms of sex distribution.

Race. A chi-square analysis investigated possible between-group differences in terms of race distribution. The results suggested that similar numbers of participants of different races were present in each of the two groups, $\chi^2(4) = 6.164$, $p = 0.187$. Interpretation of these results requires a degree of caution, however, as fewer than 80% of the data cells had frequencies

greater than 5, and the control group had no Asian or Indian participants, yielding data values of 0 in those cells.

The results from the above analyses suggest the Trauma and Control groups were well matched for the demographic characteristics of age, sex, and race. With regard to another important demographic variable, level of education, all participants in this sample were members of the UCT student population, and therefore it is probable that there were no statistically significant between-group differences in this regard.

Clinical Characteristics of the Sample

All participants completed the CTQ-SF on three separate occasions, and so received three scores on each of the CTQ-SF subscales, and three CTQ-SF total scores. To analyse between-group differences on each of these outcome variables, average scores across the three administrations were calculated for each participant. Those average scores were then used in the analyses presented in Table 2.

Table 2
Clinical Characteristics of the Current Sample (N = 38)

CTQ-SF outcome variable	Trauma (n = 16)	Control (n = 22)	t	p	Cohen's d
Total Score	53.18 (6.72)	40.88 (1.95)	7.11	< .001***	2.68
Emotional Abuse	11.08 (4.11)	7.09 (1.23)	3.77	< .001***	1.42
Physical Abuse	8.05 (2.62)	5.61 (0.87)	3.58	< .01**	1.34
Sexual Abuse	6.72 (2.52)	5.08 (0.25)	2.60	< .01**	1.00
Emotional Neglect	11.96 (4.30)	7.09 (1.54)	4.33	< .001***	1.62
Physical Neglect	7.25 (2.46)	5.68 (0.85)	2.44	< .05*	0.92

Note. Means are presented with standard deviations in parentheses. CTQ-SF = Childhood Trauma Questionnaire – Short Form. All t-tests are 1-tailed, calculated with separate variance estimates.

As the table shows, a series of one-tailed t-tests was performed on the data. The *a priori* prediction here was that the Trauma and Control groups would differ significantly across all the outcome variables of the CTQ-SF, and that, more specifically, participants in the Trauma group would show significantly higher scores than those in the Control group on all of the outcome variables. For all comparisons, the assumption of homogeneity of variances was not upheld, and therefore separate estimates of variance were used. As expected given the study's inclusion

criteria, and as shown in the table, there were statistically significant between-groups differences in the expected direction on all of the CTQ-SF outcome variables.

The effect size is a measure of the size of the difference between two variables (Cohen, 1988). Results for effect sizes reported in the table show that the between-groups differences on all the CTQ-SF outcome variables are quite large (for all comparisons, $d > 0.9$).

According to the descriptive severity ratings for the CTQ-SF subscale scores (see Table A1 in Appendix A), participants in the Trauma group received, on average, "low to moderate" scores on all the subscales except Physical Neglect (PN). For PN, the Trauma group achieved, on average, a "none to minimal" rating. The Control group received, on average, "none to minimal" ratings on all the subscales, as was expected. Despite both groups being in the same descriptive range for PN, the Trauma group still had significantly higher average scores on this subscale. These findings therefore confirm the *a priori* predictions for these data.

Test-Retest Reliability of the CTQ-SF

In order to estimate the test-retest reliability of the CTQ-SF, Pearson's correlations were computed across three questionnaire administrations. The interval between administration 1 and administration 2 (Interval I) lasted on average 9 weeks ($M = 8.636$, $SD = 9.373$), while the interval between administration 2 and administration 3 (Interval II) lasted on average 11 weeks ($M = 10.833$, $SD = 6.337$). The interval between administration 1 and administration 3 (Interval III) obviously had the longest average time-span in weeks ($M = 18.818$, $SD = 10.505$).

Table 3 presents the relevant correlation coefficients. The Trauma and Control group data were collapsed to have CTQ-SF outcome variable scores for the entire sample. Participants who had missing data for any of the three administrations were excluded from the analysis, leaving a total sample size of $N = 29$.

Table 3
CTQ-SF Test-Retest Reliability Estimates (N = 29)

CTQ-SF outcome variable	Interval I	Interval II	Interval III
Total Score	.80*	.84*	.76*
Emotional Abuse	.88*	.77*	.75*
Physical Abuse	.89*	.80*	.73*
Sexual Abuse	.89*	.58*	.83*
Emotional Neglect	.87*	.87*	.87*
Physical Neglect	.38*	.37*	.29

Note. CTQ-SF = Childhood Trauma Questionnaire - Short Form. Data presented are Pearson's correlation coefficients (*r*). Interval I = time between administration 1 and administration 2; Interval II = time between administration 2 administration 3; Interval III = time between administration 1 and administration 3.
*$p < .05$.

The results show statistically significantly high positive correlations (varying between r = .37 and .89) for most of the CTQ-SF subscales across time. Not taking into account the PN correlations, which were the lowest and are discussed in more detail below, correlations for the five remaining outcome variables ranged between .73 and .89, with only the Sexual Abuse (SA) Interval II correlation falling below this range. These figures can be interpreted as follows: Those correlations ranging from .29 to 38, that is, all PN correlations, are regarded as low, and as representing a definite but small relationship. The correlation for SA Interval II (r = .58) is regarded as moderate in strength and is indicative of a substantial relationship between the variables measured. Finally, the remaining correlations, all of which range between .73 and .89, are regarded as high, and as representative of a strong relationship between the variables measured (Tredoux & Durrheim, 2002). For the most part, then, these statistics are suggestive of very good test-retest reliability for the instrument.

The original long form of the CTQ (consisting of 70 question items) showed similar test-retest reliability over a 2- to 6-month interval (Bernstein et al., 1994), a similar time span as covered in the current study. Specifically, the results showed an intraclass correlation (ICC; a type of correlation that measures the degree of relationship between units that are organized into groups) of .88. Subsequent research found similar figures for the CTQ subscales ranging from correlations of .79 to .86 over an average of 4 months (Bernstein & Fink, 1998). There are no published data on the test-retest reliability of the CTQ-SF.

With regard to the PN subscale, it appears that within the current sample responses to items on this subscale were not as consistent as those on other subscales. For instance, the only correlation that was not statistically significant was that for PN Interval III. Furthermore, as the Table shows, even at shorter intervals the PN scores produced much lower test-retest reliability estimates than did the other outcome variables.

Another out of the ordinary finding was the comparatively low test-retest reliability estimate of the Sexual Abuse (SA) subscale for Interval II (r = .58, compared to .89 and .83 for Interval I and Interval III, respectively). Because this was not the interval with the longest time-span between sessions, the length of time between administrations cannot account for this pattern of findings on the SA subscale. A more viable explanation may be related to the method of questionnaire delivery.

Method of delivery. In the first testing session of the current study, the CTQ-SF was administered using an online questionnaire. Subsequent administrations involved traditional paper-and-pencil methods. If there were differences in the quality of data retrieved from either of these methods, it should be revealed in the differences in correlation between the scores obtained across the different administrations. Specifically, if the quality of data is different for the online questionnaire (administration 1) compared to data retrieved via traditional methods (administration 2), then the Interval I correlations should be significantly different from the Interval II correlations, given that the same method (paper-and-pencil) was used for administrations 2 and 3. In addition, there should be no difference between the Interval I and Interval III correlations, because both correlations reflect associations between scores collected using different methods of delivery.

Dependent samples t-tests showed there was a statistically significant difference between correlations at Interval I (M = 0.783, SD = 0.202) compared to those at Interval III (M = 0.703, SD = 0.210), t (5) = 3.379, p = 0.0197. There were no other statistically significant differences for any of the other interval comparisons, however. This pattern of data suggests that method of delivery did not influence the degree of correlation between testing sessions, but rather that time-span between sessions may have had an influence on the overall results (although, curiously, not on the SA subscale taken alone, as noted above).

In summary, the results presented thus far have shown that the Trauma and Control groups were well matched on major demographic characteristics, and that participants in the two

groups were had significantly different trauma histories, as measured by the CTQ-SF. Further analyses of the CTQ-SF data showed excellent test-retest reliability for at least four of the five subscales, and on the instrument's total score, over the three administration occasions.

Testing Hypothesis 1: Between-group differences in BIS/BAS sensitivity

The first hypothesis of the current study was that adults with a history of childhood trauma would have heightened BIS sensitivity when compared to adults without such a history. That is, I predicted that participants in the Trauma group would score significantly higher on the BIS scale of Carver and White's (1994) BIS/BAS instrument than those in the Control group. Because BAS sensitivity is unrelated to BIS activation, and BAS is not implicated in high anxiety groups, such as individuals who have experienced early adversity, no significant between-group differences were predicted on the BAS scale. That is to say, the set of *a priori* predictions (and non-predictions) rested on the fact that Trauma participants would show evidence of an overactive BIS because of their history of exposure to traumatic events; the Control participants, with no such history, would show no such evidence.

Four independent samples *t*-tests were conducted to analyse the BIS/BAS data. Table 4 presents the results from those analyses.

Table 4

BIS/BAS Data: Between-groups differences

Outcome variable	Trauma (n = 14)	Control (n = 22)	t	p	Cohen's d
BAS					
Drive	8.929 (1.890)	8.500 (1.310)	0.796	.216	.28
Fun Seeking	7.929 (2.018)	7.773 (1.428)	0.273	.393	.09
Reward Responsive	7.143 (1.916)	7.545 (1.563)	-0.683	.250	-.24
BIS	14.214 (2.723)	14.591 (2.826)	-0.391	.349	-.14

Note. Means are presented with standard deviations in parentheses. BIS = Behavioural Inhibition Sensitivity; BAS = Behavioural Approach Sensitivity. All *t*-tests were 1-tailed and calculated using pooled variance estimates.

The table shows that the means and standard deviations for both the BIS and BAS scales were similar across the two groups. Results from the *t*-tests confirmed that, contrary to the *a priori* predictions, there were no statistically significantly between-groups differences on the BIS

scale. There were also no such differences on the BAS subscales. Furthermore, effect size estimates indicate relatively small variation in the the degree of between-groups differences on the BIS/BAS scales. These results suggest that participants in the two groups show similar characteristics with regard to their approach and inhibition sensitivities.

Testing Hypotheses 2 and 3: Processing bias for threat-related stimuli in the Trauma group and buprenorphine-mediated decrease in processing bias in the Trauma group

The second hypothesis of the current study was that participants in the Trauma group would show an attentional bias for threat-related stimuli (i.e., fearful faces in the Object Relocation Task) and avoidance of approach-related stimuli (i.e., angry and happy faces), perhaps because of their relatively overactive BIS. The non-confirmatory findings from analyses testing Hypothesis 1 made this prediction more tentative; nonetheless, it remained possible that attentional bias in the Trauma group might still have been evident despite the lack of between-group differences on the BIS/BAS scales.

The third hypothesis of the current study was that any increased attentional bias for threat-related stimuli in Trauma participants would be decreased by administration of the mu-opioid buprenorphine, and that this decrease would not be observed in Control participants. Clearly, then, Hypotheses 2 and 3 are closely related to one another, and so an analysis testing both of them is presented in this section.

The relevant analysis here involved data from the Object Relocation Task. Specifically, the prediction was that participants in the Trauma group would show attentional bias towards threat-related stimuli (i.e., fearful faces) and avoidance of approach-related stimuli (i.e., angry and happy faces) in the task. This means Trauma group participants should, compared to participants in the Control group, perform with less error in relocating fearful faces and more error in relocating angry and happy faces. Furthermore, the prediction was that the effect of buprenorphine activity would be to decrease the attentional bias for threat-related stimuli in Trauma participants, but would have no such impact in Control participants. The outcome variable here, then, was the deviation in millimetres between the relocated position for each face and its original position. Indices for attentional bias were derived by subtracting performance on emotional (angry/fearful/happy) faces from performance on neutral faces.

A 2 x 6 repeated-measures factorial ANOVA, with trauma profile as the between-subjects factor, allowed testing of the hypotheses. For the within-subjects factor, medication condition (placebo/medication) was collapsed with the emotional faces conditions (anger/fear/happy) giving a general performance for the Object Relocation Task across the medication and placebo conditions. Thus, each participant received six scores, three scores under the placebo condition (one for each of the types of emotional faces), and three scores under the medication condition (again, one for each of the types of emotional faces).

Table 5 presents the descriptive statistics for the data analysed using the repeated-measures factorial ANOVA.

Placebo. Table 5 shows that, with regard to fearful faces in the placebo condition, participants in the Trauma group had higher mean deviation scores (and therefore performed with greater error) than participants in the Control group. This piece of data is contrary to the predictions set out in Hypothesis 2. Fearful faces represent threatening stimuli, and in individuals with high levels of anxiety, these faces should preoccupy their attention and thereby lead to more error-free performance than healthy controls. What the descriptive statistics in Table 5 suggest, instead, is an *avoidance* of threatening stimuli by Trauma group participants. (Avoidance of the threat-provoking stimuli would cause less attention to be directed at the stimuli and therefore worsen recall of the original position those faces resulting in the type of error observed in the fearful faces condition outlined here.) The results also show that, with regard to angry faces in both the placebo and medication conditions, participants in the Trauma group achieved lower error scores than participants in the Control group, suggesting a bias for angry faces. Happy faces appear to have produced similar amounts of error in Trauma and Control groups. These findings are contrary to the predictions set out in Hypothesis 2.

Curiously, this is the type of performance that high-anxiety participants achieve for tasks that are subject to conscious control mechanisms, such as the emotional Stroop task (e.g., see, van Honk et al., 1998).

Table 5
Performance on the Object Relocation Task (N = 38)

Condition/Emotion	Trauma (*n* = 16)	Control (*n* = 22)
Placebo		
Anger	21.203 (7.804)	23.623 (9.522)
Fear	23.238 (11.470)	20.895 (10.798)
Happy	24.884 (13.084)	24.288 (12.262)
Medication		
Anger	22.576 (7.696)	23.684 (10.273)
Fear	21.456 (8.401)	21.766 (9.640)
Happy	23.394 (9.462)	24.355 (10.661)

Note. Statistics are for deviation in millimetres of the position of the relocated emotional face from the position of the relocated neutral face. Means are presented with standard deviations in parentheses.

Medication. Table 5 shows that, with regard to fearful faces and in contrast to the pattern of data for the placebo condition, error scores were quite similar across groups. Further with regard to fearful faces, the Table also shows that Trauma participants had larger deviation scores in the placebo condition than in the medication condition. Finally, and also with regard to fearful faces, Table 5 shows that Control participants had larger deviation scores in the medication than in the placebo condition. In fact, it appeared that the error across the fearful faces trials increased for the Control group.

These observations stand in contrast to the predictions made by Hypothesis 3. However, they would be expected if performance on the Object Relocation Task was subject to conscious control mechanisms. Notably, the purpose of administration of buprenorphine in the present study was to reduce the processing bias observed in trauma samples so that performance is more similar to that of healthy controls in the same task. The descriptive statistics for the relocation of fearful faces in the medication condition for the Trauma and Control groups do appear more similar than those in the placebo condition.

Inferential statistics for Object Relocation Task data. Assumptions of normality of data distribution and homogeneity of variances were upheld. The omnibus *F*-test showed non-significant interaction effects for trauma profile and object relocation across medication conditions, $F(5, 180) = 0.255$, $p = .937$. The main effects for trauma profile and object relocation across medication conditions were also not statistically significant, $F(1, 36) = 0.036$, $p = .850$,

and $F(5, 180) = 0.490$, $p = .784$, respectively. It therefore appears that although the trends in observed in the descriptive statistics contradicted the predictions made by Hypotheses 2 and 3, those trends were not strong enough to deliver statistical significance.

Analyses of the data provided no statistical support for the hypotheses set out in the current study. Implications and possible explanations of these results are discussed, and recommendations for future research are made, in the following section.

DISCUSSION

The current study compared personality characteristics and cognitive functioning (specifically, attentional bias) in a sample of adults who had experienced childhood trauma (the Trauma group) and a matched healthy control group. The study also examined the possible effects of the mu-opioid agonist buprenorphine on attentional bias in the Trauma group.

The first objective explored in the current research was to examine the test-retest reliability of the CTQ-SF, an instrument widely regarded as well-suited for obtaining self-reports from adults about adverse events during childhood (Thombs et al., 2007), but for which no test-retest reliability data is currently available. The CTQ-SF was administered to the sample on three separate occasions. This allowed for reliability testing across multiple sessions, over time. The method of questionnaire delivery, and its possible effect on test performance, was analysed.

The next set of objectives explored in the current research involved three specific hypotheses: *Hypothesis 1* stated that, with regard to BIS/BAS sensitivity, I predicted that adults with a history of childhood trauma would have heightened activation of the behavioural inhibition system. This increased BIS activity would, I predicted, be reflected in relatively higher scores on the BIS dimension of Carver and White's (1994) BIS/BAS scale. No significant differences were predicted for BAS sensitivity. *Hypothesis 2* stated that, with regard to performance on the Object Relocation Task, adults with a history of childhood trauma would demonstrate an information-processing bias for threat-related stimuli and avoidance of approach-related stimuli, reflected in significantly less error for relocating fearful faces to their original locations and more error for relocating angry and happy faces to their original locations, compared to healthy matched controls. *Hypothesis 3* stated that buprenorphine would alleviate the attentional bias for fearful faces described above.

Hence, the overall aim of the research was to explore the developmental outcome of early adversity on adult information processing, while examining the possibility of intervention for trauma-related information-processing bias. Unfortunately, however, the current data did not confirm the *a priori* hypotheses with regard to personality, information-processing bias, and effects of buprenorphine. In this section, I discuss these negative findings in light of the Trauma group's performance on the CTQ-SF and the effects of severity of traumatic experiences on personality traits, information-processing bias, and mu-opioid receptor activity.

CTQ-SF Analyses

Preliminary statistical analyses confirmed the *a priori* predictions that the Trauma and Control groups would differ significantly on all the outcome variables of the CTQ-SF, with Trauma group participants scoring significantly higher than Control group participants in each case. The descriptive severity ratings for the CTQ-SF subscale scores (see Table A1 in Appendix A) indicated that participants in the Trauma group received, on average, "low to moderate" scores on all the subscales except Physical Neglect (PN). For PN, the Trauma group achieved, on average, a "none to minimal" rating. The Control group received, on average, "none to minimal" ratings on all the subscales, as was expected given our recruiting strategies. Furthermore, despite the scores of both groups being in the same descriptive range for PN, the Trauma group still had significantly higher average scores on this subscale.

Bernstein et al. (2003) constructed and validated the 28-item CTQ-SF from items that were part of the original CTQ. However, no current data are available for the test-retest reliability of the CTQ-SF, and that is why I set out to provide such data. My analyses suggested very good test-retest reliability for four of the five subscales. Specifically, the test-retest reliability of the CTQ-SF in the current study proved to be very good: There were statistically significantly high positive correlations (varying between $r = .37$ and .89) for most of the CTQ-SF subscales across time. Not taking into account PN correlations (for reasons outlined in the Results section, and discussed further below), the correlations of participant scores on the five remaining subscales across repeated administrations indicated substantial and strong agreement between responses.

The original long form of the CTQ (consisting of 70 items) showed similar test-retest reliability over a 2- to 6-month interval (Bernstein et al., 1994). Bernstein and colleagues administered the 70-item CTQ to 286 drug- or alcohol-dependent patients, and then after 2 to 6 months administered it for a second time to 40 of these individuals. The results showed an ICC of .88. Subsequent research found similar figures for the CTQ subscales, ranging from correlations of .79 to .86 over an average of 4 months (Bernstein & Fink, 1998).

With regard to the PN subscale, it is notable that scores generated low correlations over the two time intervals, and that scores at the initial administration failed to predict scores at the two subsequent administrations. This pattern of data may have arisen because of problems with

the internal validity of the neglect constructs (Gerdner & Allgulander, 2009). In a study exploring the factor structure, internal consistency, and content validity of a Swedish translation of a 53-item CTQ, the authors found four of the five subscales homogenous and internally consistent (Lundgren, Gerdner, & Lundquist, 2002). The PN subscale was the only one observed to lack homogeneity in its factor structure, and the authors criticized the content validity of some of the items on that subscale. In a similar study examining the factor structure, internal consistency, inter-correlations of subscales, and sensitivity to social desirability of the same Swedish version of the CTQ-SF, findings further suggested a lack of homogeneity for the PN subscale (Gerdner & Allgulander, 2009). The authors of both studies pointed out that the neglect constructs are theoretically vague and that the PN items should, rather than referring to "physical neglect", instead be interpreted as referring to a "lack of care" and/or a "lack of supervision". Overall, their recommendations were that that the PN scale should be revised.

Given the validity problems for the PN items pointed to by these previous studies, it is possible that the participants in the current sample interpreted those items differently at the different administrations, thus providing responses at the final administration that were not in agreement with their initial efforts.

Another out of the ordinary, albeit more curious, finding was the comparatively low test-retest reliability estimate of the SA subscale for Interval II (r = .58, compared to .89 and .83 for Interval I and Interval III, respectively). Neither length of time between administrations, nor method of questionnaire delivery was found to account for the result. It would be interesting to see how this variable performs in subsequent psychometric research.

I undertook additional analyses of the CTQ-SF data to examine whether the method of questionnaire delivery made a difference to participants' CTQ-SF responses. The initial administration was undertaken online using a web-based questionnaire, whereas subsequent administrations were undertaken using traditional paper-and-pencil questionnaires. An important mediating factor for the validity of personal disclosure is anonymity and confidentiality. Because Web-based questionnaires are responded to in private, without an experimenter present, it is possible that such delivery methods may reduce response bias emerging from social desirability effects (Huang, 2006). However, in presenting data contrary to that argument, Gosling, Vazire, and Srivastava (2004) found that, when compared with data derived from traditional methods published in the *Journal of Personality and Social Psychology* (JPSP) within the year 2002, data

retrieved using an online questionnaire appeared to be consistent with results from those traditional methods.

The results reported in the present study support the finding that Web-based questionnaires may produce data consistent with those produced by traditional survey methods. More specifically, the results showed that there was a statistically significant difference between correlations at Interval I compared to those at Interval III, while no other statistically significant differences for any of the other interval comparisons were observed. The data therefore suggest that method of questionnaire delivery did not influence the degree of correlation between testing sessions, but rather that time-span between sessions may have had an influence on the overall results.

In summary, the findings generated from CTQ-SF data analyses showed that the instrument differentiated reliably between adults with a history of childhood maltreatment and healthy matched controls across four of its five subscales. In addition, findings suggested that the method of questionnaire delivery did not affect the degree of agreement across administration intervals of the CTQ-SF subscales, but that degree of agreement was, instead, affected by differences in time-span between administration intervals.

Hypothesis 1: Between-group differences in BIS/BAS sensitivity

The analyses of BIS/BAS sensitivity in the current sample revealed that, contrary to the *a priori* prediction, there were no statistically significantly between-group differences in terms of BIS scale scores. There were also no such differences in terms of BAS subscale scores. These results suggest that participants in the two groups reported similar characteristics with regard to their approach and inhibition sensitivities. It is possible that these results are attributable to participants in the Trauma group having "low to moderate" severity ratings on most of the CTQ-SF subscales, suggesting only mild traumatic histories/experiences, and therefore reducing the possibility of subsequent developmental pathology in adult life.

There are consistent reports in the literature linking severity of early adversity, characterised by repetitive, persistent, or intense exposure to the traumatic event(s), to the development of maladaptive personality structures, cognitive biases, mood states, and behavioural tendencies in adulthood (see, e.g., Sansone & Sansone, 2007; Teicher et al., 2002, 2003). One possible mechanism underlying these maladaptive developmental paths involves a

process whereby the stress response becomes sensitized by persistent re-experiencing of the traumatic event(s). Persistent stress sensitization then results in increased stress responsiveness to threatening stimuli, and a general and chronic hyperarousal of the stress response system (Teicher et al., 2002, 2003). This heightened responsiveness and state of arousal is considered a stable trait-like feature of the personality of the victim (Perry, 1995), and it is this trait that is considered the source of anxiety and the link to an increased BIS in individuals with traumatic histories (McNaughton & Corr, 2004). It is therefore argued here that the severity of childhood traumatic experiences in the current Trauma group participants did not reach the level of severity sufficient to alter their neurodevelopment and to thereby increase BIS sensitivity.

Additionally, the current study's Trauma group was a non-clinical sample of university students. Previous research that examined the BIS/BAS scales in a similar non-clinical sample of students also found no significant differences on the BIS/BAS scales between those with elevated basal levels of the stress hormone cortisol (a measure of the HPA-axis stress response) and those with lower levels (Putman, van Honk, Kessels, Mulder, & Koppeschaar, 2004).

In contrast, the findings presented by Rosenman and Rodgers (2006) suggest that higher levels of adverse childhood experiences increase the risk of higher BIS sensitivity significantly, whereas there is no significant relationship between childhood adversity and BAS sensitivity. In that study, individuals in a large randomly-selected community sample (N = 7485) were interviewed about their history, social circumstances, personality and cognitive function, recent psychological symptoms, and substance use. The participants were also asked 17 questions, each enquiring about adverse childhood experiences. The participants' responses to these questions were then analysed against their responses on the Carver and White (1994) BIS/BAS scales, and their risk for BIS/BAS sensitivity computed as an odds ratio. The findings showed a low but significant risk (odds ratio = 1.7) for behaviour inhibition. Importantly, the authors measured the odds ratio between early adversity and BIS in subjects with the highest levels of childhood adversity. Only subjects with 5 or more adverse experiences were included in the "high adversity" category, while the rest made up the "low adversity" category. In contrast, the present study's inclusion criteria for individuals in the Trauma group required that participants achieve a moderate to severe score on at least one CTQ-SF subscale. Additionally, the highest severity rating the Trauma group received, on average, was in the "low to moderate" range. Hence, in comparing the inclusion criteria for the present study with those of Rosenman and Rodgers

(2006), it appears possible that the earlier study included a trauma group (i.e., the high adversity group) with a more severe history of adverse experiences compared to the Trauma group in the current study.

Furthermore with regard to accounting for the pattern of the current non-significant results, Putman et al. (2004a) grouped their participants according to those with elevated and those with low basal levels of cortisol. Hypercortisolism has been associated with various anxiety and depressive disorders (Teicher et al., 2002) and elevated inhibited, avoidant motivation (Putman et al., 2007); nonetheless, Putman et al. (2004a) failed to find a significant correlation between basal cortisol levels and BIS/BAS scale scores. Furthermore, in that study, the "high cortisol" group showed only moderately elevated levels (with a mean cortisol level of 12.8 nmol/l) and only moderately elevated trait anxiety. The authors stated that these levels were within the range of healthy individuals. These findings, together with those reported in the present study, suggest that Carver and White's (1994) BIS/BAS scales, in particular the BIS scale, may not be sensitive to mild-to-moderate levels of anxiety and childhood adversity in non-clinical samples of individuals.

Interestingly, the trends observed in the current BIS/BAS raw data suggest increased BAS sensitivity for the Trauma group (specifically on the "Drive" and "Fun Seeking" subscales) compared to the Control group. In contrast, the Control group scored higher on the BAS "Reward Responsiveness" subscale and on the BIS scales. The effect sizes for all these comparisons were within the small range, however, suggesting the real-world relevance of these differences are rather minimal. It would be of interest to see whether future research efforts can clarify further the relationship between CTQ-SF scores and BIS/BAS sensitivity.

In summary, the results of the present study did not provide support for the hypothesis that individuals in the Trauma group would have significantly increased BIS sensitivity relative to those in the Control group. One possibility is that participants in the current Trauma group did not have sufficiently high severity ratings on the subscales of the CTQ-SF to develop heightened BIS activation (Trauma group scores for CTQ-SF subscales: EA: $M = 11.08$, $SD = 4.11$ (severe to extreme = 16 and above); PA: $M = 8.05$, $SD = 2.62$ (severe to extreme = 13 and above); SA: $M = 6.72$, $SD = 2.52$ (severe to extreme = 13 and above); EN: $M = 11.96$, $SD = 4.30$ (severe to extreme = 18 and above); PN: $M = 7.25$, $SD = 2.46$ (severe to extreme = 13 and above)).

Hypothesis 2: Processing bias for threat-related stimuli in the Trauma group

The current data did not support the *a priori* hypothesis that Trauma group participants would show an attentional bias for threat-related stimuli (i.e., fearful faces in the Object Relocation Task) and avoidance of approach-related stimuli (i.e., angry and happy faces on the Object Relocation Task).

A model for the neurodevelopmental pathway of child trauma victims, outlined by researchers such as Teicher et al. (2003, 2002) and Perry et al. (1995), would place adults with a history of early adversity at risk for various behavioural, emotional, and cognitive disorders. However, in the current study no cognitive distortions, in the form of an information-processing bias related to emotional faces, were observed for Trauma group participants. Instead, there were no between-group differences in performance on the Object Relocation Task: participants in the Trauma and Control groups performed equally under all emotional face conditions.

One might argue that this pattern of non-significant between-group differences was to be expected in light of the fact that the groups did not differ in terms of their BIS and BAS sensitivity. More specifically, if participants in the two groups showed similar levels of BIS and BAS sensitivity, then one would expect that they would process both avoidance-related stimuli (e.g., fearful faces on the Object Relocation Task) and approach-related stimuli (e.g., angry and happy faces on the Object Relocation Task) in a similar manner—and this similar processing is exactly what the results showed.

These results for the Object Relocation Task can therefore be interpreted in light of the mild-to-moderate level of trauma severity the Trauma group reported experiencing during childhood. Otherwise stated, the severity of their adverse childhood experiences was not sufficient to produce disruptions in information-processing for emotional stimuli, resulting in performance similar to that of the Control group on the Object Relocation Task.

Hypothesis 3: Buprenorphine mediated decrease in processing bias for the Trauma group

Analyses of the effects of the mu-opioid buprenorphine on information-processing bias in adults with a history of childhood trauma provided no support for the *a priori* prediction that attentional bias for threat-related stimuli (i.e., fearful face on the Object Relocation Task) in Trauma participants would be decreased by administration of the drug, and that this decrease would not be observed in Control participants.

The *a priori* prediction was made in the knowledge, based on previous literature, that endogenous opioids such as buprenorphine reduce expression of the fear response in individuals with traumatic histories by dampening the autonomic fear response and blunting the affective component of stress (see, e.g., Drolet et al., 2001; Panksepp, 2003). As noted above, however, Trauma-group participants in the current study did not have histories of severe childhood adversity; they also did not exhibit any personality-related differences compared to control participants, or respond differently to emotional stimuli. It was therefore more difficult to examine any effects buprenorphine may have had on the performance of those participants, given that the drug works by offsetting a hyper-sensitive stress response and the current Trauma participants may not have had such a disordered physiological status. However, despite the non-significant inferential statistical findings, the descriptive trends in the data are to be noted.

The descriptive data show the Trauma group committed less error in relocating fearful faces in the medication condition, compared to that groups' performance in the placebo condition. These results were contrary to the predictions made in Hypothesis 3, namely, that any increased attentional bias for threat-related stimuli (less error in relocating fearful faces when compared to controls) in Trauma participants would be decreased (more error in relocating fearful faces relative to the Trauma groups' performance in placebo condition) by administration of the mu-opioid agonist buprenorphine.

Specifically, the findings showing less error in relocating fearful faces in the medication condition, suggest the Trauma participants exhibited increased bias for threat-related stimuli during the medication condition, reflected by the larger error scores, relative to their performance in the placebo condition. However, this piece of data may also be interpreted as the Trauma group demonstrating less *avoidance* of fearful faces in the medication condition, compared to their performance in the placebo condition. Avoidance of threat related stimuli in individuals with elevated levels of anxiety is associated with conscious control mechanisms in non-clinical samples (Bar-Haim et al., 2007; van Honk, et al., 1998). Thus, the more anxiety an individual feels the more that individual consciously avoids anxiety-provoking stimuli. The descriptive findings for buprenorphine effects on attentional bias may therefore be interpreted to suggest that the mu-opioid agonist did exert anxiolytic effects in the Trauma group, resulting in the group requiring less conscious avoidance of the threat-related stimuli. This conclusion is however tentative, and requires further investigation.

Limitations and Directions for Future Research

A primary limitation of the present study is the Trauma groups' relatively moderate severity of traumatic experiences in childhood. The moderate nature of this group's average severity rating on the CTQ-SF suggests that they may not have been subject to the range of neurodevelopmental changes that are needed to produce increased sensitivity to threat-related stimuli. Future studies should examine whether the increased severity of traumatic experiences in childhood, as measured by the CTQ-SF, is related to maladaptive BIS/BAS personality traits and biases in information processing.

A second potential limitation of the present study was the rather small sample size. Studies that have examined elevated anxiety, BIS/BAS traits, and information-processing bias have, however, used similarly-sized samples (see, e.g., Putman et al., 2004; van Honk et al., 2007, 2003, 1998; van Honk & Shutter, 2006). The descriptive results reported in the present study for the Object Relocation Task contradict the trends found by other researchers who believe this task surpasses the need for supraliminal and subliminal presentation of stimulus items (van Honk et al., 2003). Furthermore, the descriptive results for the BIS/BAS scales also showed contradictory trends from what was expected from the Trauma participants. A larger sample size would help clarify whether the performances on the Object Relocation Task observed in the present study were due to chance or to actual between-groups differences.

A third potential limitation of the current study was the fact that the measure of behavior inhibition and activation was a self-report measure. We can therefore only make indirect inferences about the actual level of activity in behavioural inhibition and activation systems. Brenner, Beauchaine, and Sylvers (2005) compared Carver and White's (1994) BIS/BAS scale to physiological markers of BIS and BAS reactivity during reward and extinction. The authors found low correlations between the BIS/BAS scales and physiological measures. The only sizeable correlation they observed was between scores on the BAS Reward Responsiveness subscale and respiratory sinus arrhythmia ($r = .37$, $p < .01$). In contrast, scores on the BIS/BAS scales correlated more strongly with scores on the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). These findings suggest that the BIS/BAS scale is more strongly

associated with self-reported measures of affect than physiological markers of reward and extinction. Future research efforts should therefore use multiple measures of the BIS and BAS constructs in order to get a clearer picture of the state of activity along those dimensions within their participants.

A fourth potential limitation of the current study is that the dosage of buprenorphine administered to the sample may have been too small to mediate attenuation of an information-processing bias. Research suggests that placebo responses, in particular placebo analgesia, may share a similar neural network to the endogenous opioid system (Petrovic, 2005). The placebo in the present research may therefore have caused similar activation levels as buprenorphine, given the current dosage (0.2mg). Future research would therefore need to increase the dosage in naïve individuals; however it would have to do so ethically, that is, without increasing negative side-effects. The answer may be to use a mu-opioid receptor blockade as the control condition, not placebo. mu-Opioid receptor blockers are drugs that bind to but do not activate the mu-opioid receptor (e.g., see, Krishnan-Sarin, Wand, Li, Potoghese, & Froehlich, 1998), thereby controlling for possible placebo effects on those receptors.

Finally, the overarching research study, of which this forms part, constitutes a first step in investigating the use of new generation opioids in certain psychiatric disorders. Research using such opioids in opioid naïve individuals is almost non-existent – hence the decision to start with a sample of essentially healthy controls (i.e., no psychiatric morbidity) who were only differentiated on self-reported level of exposure to early social trauma. This may help explain why the Trauma group responded with relatively 'mild' severity ratings, and the resultant null findings. As the program progresses, participants with more severe clinical pathology will be included – but the current sample was decided on ethical principles.

Conclusion and Implications

The current study compared personality characteristics and cognitive functioning (specifically, attentional bias) in a sample of adults who had experienced childhood trauma (the Trauma group) and a matched healthy control group. The study also examined the possible effects of the mu-opioid agonist buprenorphine on attentional bias in the Trauma group.

The data presented in this thesis showed that, as a measure of childhood trauma, the CTQ-SF generated good test-retest reliability on four of its five subscales over variable lengths

of time, even given different methods of survey delivery across administrations. In addition, I found that participants with a history of childhood trauma did not differ from matched controls with regard to the current study's indices of behavioral approach and inhibition, and with regard to attentional bias. Furthermore, buprenorphine demonstrated no observable alleviation of attentional bias in individuals with histories of early adversity. One possible explanation for the lack of between-group differences may be related to the moderate severity of adverse experiences reported by the Trauma group.

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APPENDIX A

Guidelines for Interpretation of CTQ-SF Scores

Table A1

	Severity Rating			
CTQ-SF Subscale	None or minimal	Low to moderate	Moderate to severe	Severe to extreme
Emotional Abuse	5-8	9-12	13-15	16 and above
Physical Abuse	5-7	8-9	10-12	13 and above
Sexual Abuse	5	6-7	8-12	13 and above
Emotional Neglect	5-9	10-14	15-17	18 and above
Physical Neglect	5-7	8-9	10-12	13 and above

APPENDIX B

The Childhood Trauma Questionnaire-Short Form

Patient Name					Week		Visit		Date	DD	MMM	YYYY

Childhood Trauma Questionnaire – Short Form (CTQ-SF)

Instructions: These questions ask about some of your experiences growing up **as a child and a teenager**. For each question, circle the number that best describes how you feel. Although some of these questions are of a personal nature, please try to answer as honestly as you can. Your answers will be kept confidential.

When I was growing up, …	Never True	Rarely True	Sometimes True	Often True	Very Often True
1. I didn't have enough to eat.	1	2	3	4	5
2. I knew there was someone to take care of me and protect me	1	2	3	4	5
3. People in my family called me things like "stupid", "lazy", or "ugly".	1	2	3	4	5
4. My parents were too drunk or high to take care of me.	1	2	3	4	5
5. There was someone in my family who helped me feel important or special.	1	2	3	4	5
6. I had to wear dirty clothes.	1	2	3	4	5
7. I felt loved.	1	2	3	4	5
8. I thought that my parents wished I had never been born.	1	2	3	4	5
9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	1	2	3	4	5
10. There was nothing I wanted to change about my family.	1	2	3	4	5
11. People in my family hit me so hard that it left bruises or marks.	1	2	3	4	5
12. I was punished with a belt, a board, a cord, or some hard object.	1	2	3	4	5
13. People in my family looked out for each other.	1	2	3	4	5
14. People in my family said hurtful or insulting things to me.	1	2	3	4	5
15. I believe that I was physically abused.	1	2	3	4	5
16. I had the perfect childhood.	1	2	3	4	5

17. I got hit or beaten so badly that it was noticed by someone like a teacher, neighbour, or doctor.	**1**	**2**	**3**	**4**	**5**
18. I felt that someone in my family hated me.	**1**	**2**	**3**	**4**	**5**
19. People in my family felt close to each other.	**1**	**2**	**3**	**4**	**5**
20. Someone tried to touch me in a sexual way, or tried to make me touch them.	**1**	**2**	**3**	**4**	**5**
21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	**1**	**2**	**3**	**4**	**5**
22. I had the best family in the world.	**1**	**2**	**3**	**4**	**5**
23. Someone tried to make me do sexual things or make me watch sexual things.	**1**	**2**	**3**	**4**	**5**
24. Someone molested me.	**1**	**2**	**3**	**4**	**5**
25. I believe that I was emotionally abused.	**1**	**2**	**3**	**4**	**5**
26. There was someone to take me to the doctor if I needed it.	**1**	**2**	**3**	**4**	**5**
27. I believe that I was sexually abused	**1**	**2**	**3**	**4**	**5**
28. My family was a source of strength and support.	**1**	**2**	**3**	**4**	**5**

APPENDIX C

The BIS/BAS Scale

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all the items; do not leave any blank. Choose only one response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses.

1) A person's family is the most important thing in life.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

2) Even if something bad is about to happen to me, I rarely experience fear or nervousness.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

3) I go out of my way to get things I want.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

4) When I'm doing well at something I love to keep at it.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

5) I'm always willing to try something new if I think it will be fun.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

6) How I dress is important to me.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

7) When I get something I want, I feel excited and energized.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

8) Criticism or scolding hurts me quite a bit.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

9) When I want something I usually go all-out to get it.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

10) I will often do things for no other reason than that they might be fun.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

11) It's hard for me to find the time to do things such as get a haircut.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

12) If I see a chance to get something I want I move on it right away.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

13) I feel pretty worried or upset when I think or know somebody is angry at me.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

14) When I see an opportunity for something I like I get excited right away.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

15) I often act on the spur of the moment.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

16) If I think something unpleasant is going to happen I usually get pretty "worked up."

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

17) I often wonder why people act the way they do.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

18) When good things happen to me, it affects me strongly.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

19) I feel worried when I think I have done poorly at something important.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

20) I crave excitement and new sensations.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

21) When I go after something I use a "no holds barred" approach.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

22) I have very few fears compared to my friends.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

23) It would excite me to win a contest.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

24) I worry about making mistakes.

1	2	3	4
very true for me	somewhat true for me	somewhat false for me	very false for me

APPENDIX D

Telephonic Screening Questionnaire and Brief Verbal Consent Form

PARTICIPANT TELEPHONIC SCREENING QUESTIONNAIRE

DATE: _____

A. Personal Details:

Full Name: _____
Date of Birth: _____
Gender: _____
Occupation: _____
Student number: _____

B. Contact Details:

Address: _____
_____
_____

Tel. number (h) : _____
(w): _____
(c) : _____

Email Address: _____

C. Medical Details: *Please circle*

1. Are you right-handed? Yes / No

2. Do you take any kind of medication on a regular basis? Yes / No
   If yes, please specify what kind
_____

3. Are you allergic to any medication? Yes / No
   If yes, please specify what kind
_____

4. Have you ever had a head injury? Yes / No
   If yes, describe most severe:_____

Were you knocked unconscious? Yes / No
If yes; how long? _____

Any surgery/hospitalisation as a result of your head injury? Yes / No
If yes; please specify:_____

5. Do you have a metal object in your body (eg. aneurysm clip)? Yes / No
If yes, please specify:_____

6. Do you wear a metal prosthesis (eg. artificial leg)? Yes / No
If yes, please specify: _____

7. Do you have a pace-maker? Yes / No

8. Have you ever been diagnosed with asthma? Yes / No

9. Have you ever been diagnosed with chronic bronchitis, emphysema, or any other respiratory problems? Yes / No

10. Have you ever been diagnosed with a hepatic (liver) problem/disorder? Yes / No

11. If you are female, are you currently pregnant? Yes / No

- If you are female and answered no to question 10, are you planning on becoming pregnant within the next year? Yes / No

12. If you are female, are you currently a breastfeeding mother? Yes / No

13. Have you ever been diagnosed with a renal problem / disorder? Yes / No

14. Have you ever had seizures or an epileptic fit? Yes / No

15. Has anyone in your immediate family (siblings, parents) ever been diagnosed with epilepsy? Yes / No
If yes, please specify who: _____

16. Have you ever been diagnosed with a psychiatric illness? Yes / No
If yes, please specify: _____

17. Have you ever had any neurological condition? Yes / No
If yes, please specify: _____

18. Other notes:

_____

_____

_____

_____

_____

Brief Telephonic Verbal Consent Form

This study is entitled 'Functional brain imaging in healthy participants with a history of early adversity'. It will look at the effects of the opioid, buprenorphine, on brain function. You will be administered a small dose of buprenorphine on 2 occasions. You will also perform neuropsychological tasks, undergo brain imaging, and have blood drawn for genetic testing.

Please circle

1. At this stage, do you consent to participate in this study? Yes / No

2. Do you acknowledge that all of the details (eg age & medical details) given to the researcher by you are correct? Yes / No

3. Are you satisfied that any questions that you may have at this stage have been appropriately answered? Yes / No

APPENDIX E

F-MRI Participant Information Leaflet and Consent Form

TITLE OF THE RESEARCH PROJECT: Functional brain imaging in healthy subjects with a history of early adversity.

PROTOCOL NUMBER: OP-0307

REFERENCE NUMBER: **M07/03/010**

PRINCIPAL INVESTIGATOR: Professor Dan J Stein

ADDRESS: MRC Anxiety & Stress Research Unit, University of Stellenbosch Department of Psychiatry/ University of Cape Town Department of Psychiatry

CONTACT NUMBER: +27 21 938-9228

Dear Volunteer

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the Committee for Clinical Trials at Stellenbosch University and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

If you receive this invitation to participate, you will already have given your consent/assent to participate in the part of this study that is assessing the effect that Buprenorphrine has on individuals who have experienced a childhood traumatic event.

STUDY PROCEDURES

At each visit, besides getting the study medication from your doctor and being asked to complete the questionnaires and tasks, if you are agreeable you will have a type of brain scan, called an fMRI (functional magnetic resonance imaging) scan. As the scan is done in a relatively confined space, occasionally people become anxious. This does not happen often, and if you feel anxious, we will spend time allowing you to get used to the surroundings. During the scan, you will be asked to perform some simple tasks of memory and attention, which will enable the investigators to determine your brain function. The scan will require you to lie on your back on a table that will move into the scanning machine for the hour it will take for the scan. During this time you

will be able to close your eyes and rest. You will also be able to talk to the study doctor/assistant at all times during the scan if you should experience any discomfort. The scan is a safe procedure if you have been screened correctly for the presence of any magnetic material on or inside you such as pace-makers, surgical clips and metal objects in the eyes. A formal screen for this will be done at the screening visit by a member of the study team. When the magnet in the machine is switched on, it will make some loud banging noises, but you will be clearly warned when this will take place. At this time you will feel nothing and the noise is not harmful to you in any way. To minimise the possible discomfort associated with this, we will give you some soft earplugs to put in .

DISCOMFORT ASSOCIATED WITH THE STUDY

There are only low or minimal risks associated with your participation in this study. If you feel tired at any point in any of the visits, you should please ask your study doctor/psychologist for a rest. If for some reason you are unable to complete a visit on a particular day we may reschedule to complete the assessments at another time.

POTENTIAL BENEFITS

There may be no direct benefits to you for participating in this study. However, you will be making an important contribution to this research that may benefit others in the future. We expect that the results of this study will help us understand the effects of apathy and depression on brain shape as well as memory and concentration.

COMPENSATION FOR STUDY PARTICIPATION

While you will not be paid to take part in this study, all evaluations will be provided at no cost to you or your medical aid. We will however pay you for any cost incurred in attending the prescribed study visits.

CONFIDENTIALITY

Your participation is regarded as strictly confidential. The results of the study will be published in the professional literature and made available to of the Committee for Human Research of Subcommittee C at the University of Stellenbosch, but your identity will not be revealed at any time to people outside of the study team.

THE RIGHT TO ASK QUESTIONS/WITHDRAW FROM THE STUDY

You have the right to ask questions at any time about any aspect of the study. If you have any queries, you can contact:

Dr S Seedat: Tel (24hr contact number): 082-784-8148
Dr P Carey: Tel (24hr contact number): 083-700-0046
Dr D Stein: Tel (24hr contact number): 083- 263-9679

Your participation in the study is entirely voluntary. You have the right to withdraw at any time. If you decide to withdraw from the study, it will not jeopardize you or any future treatment you may require in any way.

You are entitled to a signed copy of this document.

If you agree to take part, please complete the following section.

I)……. have been invited to take part in the above research project entitled Functional brain imaging in healthy subjects with a history of early adversity.
The study doctor/nurse have explained the details of the study to me and I understand what they have said to me.
They have also explained that this study will involve up to 5 assessments which include interviews, filling questionnaires, a physical examination including a blood test, and brain scan.
I also know that I am free to withdraw from the study at any time if I am unhappy.
By writing my name below, I voluntary agree to take part in this research project. I confirm that I have not been forced in any way or by anyone to take part.

Name of Participant (printed)

Signature of Participant Dated

Declaration by investigator

I (name) ……..…… declare that:

I explained the information in this document to ……..
I encouraged him/her to ask questions and took adequate time to answer them.
I am satisfied that he/she adequately understand all aspects of the research, as discussed above
I did/did not use an interpreter (if an interpreter is used, then the interpreter must sign the declaration below).

Signed at (place) .....…..…….. on (date) ……...……...

Signature of investigator

Declaration by interpreter

I (name) ……..…… declare that:

I assisted the investigator (name) …….……. to explain the information in this document to ……..……... using the language medium of Afrikaans.
We encouraged him/her to ask questions and took adequate time to answer them.
I conveyed a factually correct version of what was related to me.

I am satisfied that the parent/legal guardian fully understands the content of this informed consent document and has had all his/her questions satisfactorily answered.
Signed at (place) .....…..……. on (date) ……...…….. 2010

Signature of interpreter

APPENDIX F

Participant Information leaflet and Consent Form

TITLE OF THE RESEARCH PROJECT: *Functional brain imaging in healthy subjects with a history of early adversity*

PROTOCOL NUMBER: OP-0307

REFERENCE NUMBER: M07/03/010

PRINCIPAL INVESTIGATOR: Professor Dan J Stein

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You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the Committee for Clinical Trials at Stellenbosch University **and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.**

This trial is being run at the Department of Psychiatry, University of Stellenbosch. We aim to recruit a total of 40 participants over a period of 2 years

What is this research study all about?

The purpose of this study is to find out what effects Buprenorphrine has on individuals who have experienced a childhood traumatic event. This study will make comparisons between treatments. Randomisation means that the participants are put into treatment groups by chance. The groups are selected by a computer that has no information about the individual participants. Participants in each group (Buprenorphrine or placebo) then have a different treatment and their responses are then compared.

In a blinded study the treatment provided will be hidden or concealed so you will not know which treatment you will receive. This research study is called "double blind". In a double blind

research study neither you nor your study doctor will know in which treatment group you are (although if your doctor needs to find out he/she can do so).

A placebo is a dummy treatment such as a pill or a capsule, which looks like the real thing but is not. Placebo medications do not contain active ingredients.

In a crossover study you will first receive one treatment and then the other. If you agree to take part in this study you will be given either Buprenorphrine or placebo on one visit and the other (either Buprenorphrine or placebo) on the following visit.

Procedures

If you agree to take part in the study and if you meet all of the conditions required to enter the study, you will have the following tests and procedures:
At the first clinic visit the study investigator will ask you some questions to determine whether you suffer from any psychiatric disorders. If you are eligible and agree to participate in the study you will be asked to attend the clinic on up to 4 more occasions. You will receive study medication or placebo from the study nurse on the day of your visit. You will then be asked to complete questionnaires. You will also be asked to complete some computerised tasks, and will have a brain image scan done0839638265 during some of the sessions (if you agree to do so).

At each visit a record will be kept of any medications that you are taking currently or have taken recently. A record will also be taken of any side effects that you may be experiencing.

Blood samples (about 30 ml [6 tablespoons]) will be collected for routine laboratory testing, for a pregnancy test (if you are female) and for possible future genetic studies.
You will be asked to have your blood drawn on the first day of attendance. Approximately 12ml of blood will be drawn from your arm. We may need to contact you again to get another blood sample should we fail to get a DNA sample from your blood. The blood sample you give may be used to create a cell line. This is done by changing some of your blood cells so that they can grow forever. The cell line is living tissue and it can be used to make more of your DNA at any time in the future. Candidate polymorphisms identified to be associated with anxiety or depression and possibly playing a role in explaining variance in the fMRI results will be investigated later on. This process will take place at the MRC Centre for Molecular and Cellular Biology and the Division of Medical Biochemistry, Faculty of Health Sciences, at the University of Stellenbosch, as well as at the Centre for Proteomics and Genomics Research (CPGR) at the University of Cape Town. The DNA will then be taken from the cell line and saved for scientific analyses which will be performed now, and possibly in the future.

We may contact you later for further information, or request you to complete another interview at a later date, in order to obtain follow-up information that may be of use in our genetic analyses. This may involve an assessment similar to the current assessment, including a series of interviews and/or another blood sample. Your current participation is in no way binding to your future participation.

Your cell line and DNA will be maintained permanently, unless you request to have it removed. If at any time in the future you wish to have your DNA, cell lines or clinical data removed from the storage site, you may do so by contacting the researchers conducting this study.

Why have you been invited to participate?
You have been invited to participate in this study because you may have been exposed to a traumatic event in your childhood. We would like to see if this medication will impact differences in people's performance on certain tasks which may be associated with having experienced early adversity.

What will your responsibilities be?
The study investigator will be required to ask you about medications that you may be taking currently or that you may have taken recently. Your study investigator will explain to you which medications need to be stopped during the entire length of the study and how soon before you take part in the study these medications must be stopped.

Your doctor will also advise you on which prescription or over-the-counter medications or any other remedies or foods that you will be required to either stop or restrict your consumption of during the entire length of the study. This will include a restriction on the amount of alcohol that can be consumed.

At each visit you may be asked to complete questionnaires or tasks to check the status of your symptoms. These will measure your mood, emotional responses, trust, sociability and emotional resilience.

Will you benefit from taking part in this research?
Your participation in this study will add to the medical knowledge about the use of this medicine.

The information learned from this study may help to establish a new medication for the treatment of people who have been exposed to trauma in their childhoods.

Are there in risks involved in your taking part in this research?
All drugs and even placebos may cause side effects in some people. There may be risks, inconveniences or side effects that are not known at this time.

The most commonly reported adverse reactions of Buprenorphrine administration are constipation, headaches, insomnia, asthenia, drowsiness, nausea and vomiting, fainting and dizziness, orthostatic hypotension, sweating.

Special caution should be exercised when driving or using machinery since the study medication may cause drowsiness.

You will receive both Buprenorphrine and placebo, each at a separate visit. As mentioned earlier this research study is called "double blind". In a double blind research study neither you nor the study investigator will know in which treatment group you are. It is possible that you may not experience any side effects when receiving treatment. This does not mean that you have received placebo. Similarly, even if you do receive placebo you may experience some side effects which you and your doctor feel could be associated with the study drug.

Because the effects of Buprenorphrine on the unborn foetus (child/baby) or nursing baby/infant are uncertain, you will not be allowed to enter this study if you are pregnant or breastfeeding or planning to become pregnant within 6 weeks of your screening visit.

If you choose to participate in this study, you must use one of the allowed contraceptive methods (a way to prevent you from becoming pregnant) for the specified period of time before and after you enter the study. Ask your doctor if you have any questions about these choices and which might be best for you.

Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of your doctor, are as follows:

a Non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including being post-menopausal. For purposes of this study, postmenopausal is defined as one year without menses); or

b Child-bearing potential, you must agree to one of the following:
- Male partner who is sterile prior to your entry into the study and is your sole sexual partner;
- Oral contraceptives (either combined or progestogen only);
- Double-barrier method of contraception consisting of spermicide with either condom or diaphragm;
- IUD with a documented failure rate of less than 1% per year; or

Even when you use one of the allowed contraceptive methods, there may be a small risk that you could become pregnant. Because of this, you will be tested during the study to see if you are pregnant. If one of these tests shows that you have become pregnant, your unborn baby may have been exposed to Buprenorphrine even if you stop taking the drug right away. So, if you think you are pregnant or may become pregnant, you must tell Dr_____ at the earliest opportunity. If you should become pregnant during the study you will be asked, required or requested to, stop taking the study drug immediately. You will also be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy must be reported to your study doctor.

There may be other risks, inconveniences and side effects to the embryo, foetus (unborn child), or nursing infant that are unknown at this time.

If you do not agree to take part, what alternatives do you have?

Before you decide whether or not to take part in this study, you may wish to consider other treatment options. Your study doctor will describe these to you based on your medical history and the treatment you have received to date.

Who will have access to your medical records?
Maintaining your confidentiality is important. Your personal information (for example your gender, age, the details of your medical conditions) and other information (the data collected by the investigators as part of the study) will be identified by a number (i.e., coded). Your name will not appear in any publications or reports produced from this study. The investigators will keep the information and the results collected about you in this study. This information about you will be kept in a secure place. By agreeing to take part in this study, you will be allowing certain persons to see the information about you (both personal, including your name, and other information) held by the study doctor. You have the right to withdraw your consent to participate in this study at any time. If you withdraw your consent to participate in this study no new information will be collected from you and added to existing data or to a database. Your information will be processed electronically (i.e., by a computer) or manually and analysed to determine the outcome of this study. Your information may/could be sent to regulatory authorities and to the Ethics Committees. You have the right to ask the study doctor about the data being collected on you for the study and about the purpose of this data. You have the right to ask the study doctor to allow you to see your personal information and to have any necessary corrections made to it.

What will happen in the unlikely event of some form of injury occurring as a direct result of your taking part in this research study?
If you become ill or injured as a result of participation in this clinical study, you will be referred for appropriate medical treatment. The University of Stellenbosch's insurance policy will cover the costs of such treatment. If you have any questions concerning the availability of compensation/medical care or if you think you have experienced a research-related illness or injury, contact details are below.

Your right at law to claim compensation for injury where you can prove negligence is not affected. For medicines that have already been approved by the Medical Authorities to treat this condition, normal legal rules on compensation will apply.
If you have any questions about your rights as a research subject, you should contact the Committee for Pharmaceutical Trials of the University of Stellenbosch, Tel: (021) 938 9075, Fax: (021) 933-6330.

If you have questions about this trial you should first discuss them with your study doctor or the Committee for Pharmaceutical Trials of the University of Stellenbosch.
Dr S Seedat: Tel (24hr contact number): 082-784-8148
Dr P Carey: Tel (24hr contact number): 083-700-0046
Dr D Stein: Tel (24hr contact number): 083- 263-9679

After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control

Council (MCC) at: The Registrar, SA Medicines Control Council, Department of Health, Private Bag x 828, Pretoria, 0001, Fax: (012) 323 4474

Will you be paid to take part in this study and are there any costs involved?

No you will not be paid to take part in the study but your transport and meal costs (R150) will be covered for each study visit. There will be no costs involved for you, if you do take part.

Is there any thing else that you should know or do?

- **You can contact Dr ……..…..….. at tel …… if you have any further queries or encounter any problems.**
- **You can contact the Committee for Human Research at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study doctor.**
- **You will receive a copy of this information and consent form for your own records.**

Declaration by participant

By signing below, I ……..…… agree to take part in a research study entitled *(insert title of study)*.

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) .....…..…….. on (*date*) ……...…….. 2010.

…… ……

Signature of participant Signature of witness

Declaration by investigator

I *(name)* ……..…… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) .....…….....…….. on (*date*) ……...…….. 2010.

…… ……

Signature of investigator Signature of witness

Declaration by interpreter

I *(name)* ……..…… declare that:

- I assisted the investigator (*name*) ……. to explain the information in this document to (*name of participant*) ……..…….. using the language medium of Afrikaans.
- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) .....…….....…….. on (*date*) ……...…….. 2010.

…… ……

Signature of interpreter Signature of witness