1 A COGNITIVE NEUROSCIENCE OF POST-TRAUMATIC STRESS DISORDER

The primary purpose of this thesis is to apply advanced electrophysiological techniques to investigate the component cognitive processes of neutral information processing in post-traumatic stress disorder (PTSD). This work applies neuroimaging techniques, primarily event-related potentials (ERPs), which have been employed to investigate various aspects of cognition (e.g., Kutas & Hillyard, 1984). ERPs are derived from the electroencephalogram (EEG) by recording short epochs that are precisely time-locked to the onset of stimulus or response events. After averaging across many such epochs, the brain activity related to a specific event type is extracted from the background noise (given the assumption that the non-event related activity is random, while the event-related signal is stable across epochs). With careful manipulation of event types, it is possible to measure modulation of the ERP signal and to infer differences in brain activity for various stimulus or response events related to different cognitive processes. ERPs provide a high temporal resolution that indicates stages or components of cognitive processes such as sensation, perception, attention and memory (see Kutas & Hillyard, 1984; Regan, 1989). These temporal dynamics of cognitive processes are not readily available from response time or volumetric neuroimaging studies. The present work employed dense scalp arrays for recording ERPs, which provide not only fine temporal resolution, but also ERP topography. This study uses topographic analysis of dense array ERPs recorded during cognitive paradigms that dissect the component structure of executive functions in PTSD. The focus of this work is the capacity of PTSD patients to process neutral information, which is critical for adaptive behavior. It will be argued and demonstrated that there are deficits in neutral information processing in PTSD.

Firstly, this chapter reviews relevant theory and research on information processing in PTSD, to give the context of the present work. There is an emphasis on information processing and neuropsychology approaches to PTSD, with some account of neurophysiology and psychophysiology of sensory, attention and working memory processes. The importance of an information processing perspective (see Bartlett, 1932, 1958; Miller, Galanter & Pribram, 1960; Mandler, 1984) may lay in not only a clearer understanding of cognition in PTSD, but also the adaptation of cognitive treatment programs to facilitate trauma recovery (e.g., Foa, 1997; cf., Allen, 1996; Post, Weiss, Smith & McCann, 1997). Also, relating information processing to neuroscience might provide a better understanding of how psychopharmacology may affect the cognitive, emotional and associated physiological processes driving the onset and maintenance of PTSD (see, Yehuda & McFarlane, 1995; McFarlane, 1997; Post et al., 1997; McFarlane, Yehuda & Clark, 2002). Hence, the following review considers information processing in PTSD from various perspectives, including cognitive studies, neuropsychology, psychophysiology and neuroimaging.

1.1 Clinical Phenomena

The precipitation of PTSD occurs during intense, overwhelming horror, fear, or helplessness in the face of life threatening circumstances, bearing witness to the injury or death of a person, or learning about serious harm to or death in a close friend or relative (American Psychiatric Association [APA], 1994). An acute reaction resolves within three months, but PTSD is a chronic and debilitating disorder that can persist for many years (APA, 1994; Warshaw et al., 1993; Yehuda & McFarlane, 1995).

A traumatic experience may precipitate PTSD, dissociation, panic attacks and depression, which are among the most common psychiatric disorders (McFarlane, 1997). PTSD may result from not only combat exposure, but also natural disasters and

various civil traumas, including motor vehicle accidents, exposure during emergency services (police, ambulance, fire), and assault or rape. The experience of any event that severely threatens or actually causes physical harm or severe emotional distress can precipitate PTSD, with some estimates indicating that PTSD affects 15-30% of persons exposed to combat or disasters (Kulka et al., 1990; Green, 1994) and 18-42% of people with physical injury, after 6 months, with decreasing prevalence over time (O'Donnell, Creamer, Bryant, Schnyder & Shalev, 2003; see also McFarlane, 1997).

Given that many people exposed to trauma do not develop PTSD, it is important to understand susceptibility to PTSD, particularly the initial impact of trauma and what differentiates those who develop PTSD from those who recover normally (e.g., Foa, 1997; McFarlane, 1997). Susceptibility to PTSD is associated with various factors, including genetic predisposition, a family history of psychiatric disorder, personality attributes, prior psychiatric disorder, prior exposure to trauma or other stressful life events, and social support, but the primary determinant of the onset and severity of PTSD is the proximity, intensity, and duration of the traumatic event (APA, 1994; McCarroll, Ursano & Fullerton, 1993, 1995; Schnurr, Friedman & Rosenberg, 1993; Goenjian et al., 1994; Koopman, Classen & Spiegel, 1994; McNally & Shin, 1995; Weine et al., 1995; Yehuda et al., 1995; Yehuda & McFarlane, 1995; Buckley, Blanchard & Neill, 2000; Seedat, Niehaus, & Stein, 2001). If the proximity, intensity, and duration of the trauma are the most important predictors of PTSD, a developmental understanding of PTSD requires assessment of the initial trauma impact on stress physiology (e.g., Kaufer, Friedman, Seidman & Soreq, 1998; Delahanty, Raimonde, & Spoonster, 2000; Pitman et al., 2002; Delahanty, Raimonde, Spoonster & Cullado, 2003; Vaiva et al., 2003), as well as emotional and cognitive systems (e.g., Foa, 1997). Furthermore, it is important to understand the enduring changes to cognitive and

emotional processes that result from the initial impact, especially as these systems adapt and recover (see Bryant, 2003).

A traumatic incident may shatter beliefs and expectations of regularity and safety. The impact of a trauma may involve a difficult process of reconciling previous experiences of safety with a traumatic experience of vulnerability - a state of cognitive dissonance that engages further attention and effort toward resolution (see Festinger, 1957). In many cases, trauma victims are susceptible to changes in important aspects of causal attribution style that can promote learned helplessness and depression (Mikulincer & Solomon, 1988; see also Seligman, Abramson, Semmel & von Baeyer, 1979; Seligman, 2002). That is, PTSD patients are susceptible to the following attitudes and beliefs: (a) negative events are external, stable, and uncontrollable, (b) the perceived lack of control of negative events promotes helplessness, and (c) their causal attributions for positive events are also external and uncontrollable, so positive experiences are not a result of their own action and therefore no source for self-esteem (Mikulincer & Solomon, 1988).

However, PTSD comprises more than merely a biased cognitive appraisal pattern, it involves difficulty with resolving intense emotional experience (see Horowitz, 1986; see also Yehuda & McFarlane, 1995; Foa, 1997). During the process of adaptation to the trauma (rather than recovery), PTSD patients can suffer numerous, persistent, often uncontrollable and intrusive, recollections of the trauma (APA, 1994). These traumatic recollections may consist of daily reminders, nightmares, and vivid flashbacks (APA, 1994). Frequent intrusive recollections of a trauma can be provoked by objects, people, places, or events that resemble or symbolize the trauma, provoking emotional distress, arousal and consequent hypervigilance for such cues (APA, 1994). The intrusions facilitate the secondary association of the trauma with a wide variety of otherwise neutral circumstances, lending greater potential to various cues for traumatic triggering

and increasing the pressure to be vigilant for diverse trauma cues. Hence, given the overwhelming intensity of the recollections, PTSD patients actively avoid situations, activities, or people and conversation related to their trauma (APA, 1994). The avoidance can be an intense emotional numbing and withdrawal, including loss of interest in previously enjoyable activities and loss of empathy and intimacy with others (APA, 1994).

Horowitz (1986) identified these states of intrusion and avoidance as a cyclical pattern of gradual adaptation to the trauma, wherein extreme tension between these states may prolong the process of resolution. Ideally, this process might be considered to be like a pendulum, swinging from extremes, until eventually it comes to rest (unless provoked by an external force). The pendulum is set in motion by the traumatic event and the duration of its motion may be concomitant with the inertia (or intensity) of the event, while avoidance may be considered an active, energetic process of insulation from further exacerbating forces. However, extreme avoidance can promote a lack of further adaptive responses and accommodation to new circumstances, leaving a person stuck in a post-trauma response pattern. This system of cognitive and emotional oscillations can be related to concepts from nonlinear, chaotic dynamics, such as local attractors, or the dynamics of complex neural networks (e.g., McFarlane et al., 2002). One path to resolving the trauma response is to initially find a point of emotional and somatic equilibrium, which can facilitate emotional engagement with the trauma and development of clear trauma narratives, and then some adjustment to different cognitive appraisal processes and life circumstances, including changes to working and family life (see Foa, 1997; see also Leys, 2000).

1.2 Cognition and Neuropsychology

PTSD has been considered to be essentially a failure to resolve cognitive and emotional responses to trauma, which may depend critically on the ability to attend to the present, neutral circumstances. Janet, a pioneer of trauma research, described the traumatic recollections of PTSD as an attachment to the trauma that cannot be resolved and replaced by new experiences; he proposed that PTSD patients are not only,

> *unable to integrate traumatic memories, they seem to have lost their capacity to assimilate new experiences as well. It is . . . as if their personality, which definitely stopped at a certain point, cannot enlarge any more by the addition or assimilation of new elements. (Janet, 1911, p. 532, cited in van der Kolk, Herron, & Hostetler, 1994, p. 584).*

Janet proposed that traumatic experiences remain encapsulated within their own psychic arena, dissociated from a plethora of memories, feelings, and thoughts about normal experiences (van der Kolk et al., 1994; see also Leys, 2000). He proposed that effective treatment requires translation of the dissociative traumatic representations into narratives, often through the use of hypnotic states and suggestions, which allow direct manipulation of the trauma experience. Moreover, he proposed it is important to develop and encourage alternative, non-trauma mental states and the ability to attend to the present (see Leys, 2000; cf. Foa, 1997).

The intensity of a traumatic experience leaves an episodic memory trace of salient sensations, perceptions, emotions, and reactions that are encapsulated into a trauma schema (Bartlett, 1932, 1958; Mandler, 1984; Foa, Steketee, & Olasov-Rothbaum, 1989). However, unlike most episodic memories that have a high degree of spatio-temporal coherence, the overwhelming emotional responses can provoke dissociative states that fragment the experience from integrated evaluation and processing in the context of normal cognitive schemata (van der Kolk, 1997). These fragmented sensory,

emotional and cognitive representations are not translated into linguistic representations that can be easily manipulated in thought, but remain primary sensory and emotional representations that can be reactivated to recreate almost identical states to those experienced during the trauma (van der Kolk, 1997; cf. Leys, 2000). This intrusive reexperiencing again overwhelms normal cognitive states - the energy involved can lead to sensitization and further persistence of the traumatic experiences, both emotional and cognitive, with the potential for greater elaboration and consolidation across successive intrusions (see Kolb, 1987; McFarlane et al., 2002). In PTSD there is a dissociation of traumatic from normal experience and the traumatic content becomes encapsulated into a sensitive, coherent, and stable trauma schema, incorporating sensory, affective, semantic and intentional experience (Chemtob, Roitblat, Hamada, Carlson, & Twentyman, 1988; McFarlane et al., 2002; see also Lang, 1978, 1985).

Activation of this trauma schema encourages PTSD patients to interpret experience in terms of that schema and to develop an expectancy that threatening or traumatic events will occur; so PTSD patients are susceptible to interpret ambiguous events as threatening (Chemtob et al., 1988). For example, this physiological, emotional and cognitive sensitivity to threat in PTSD is associated with a heightened startle response to sudden loud tones (Butler et al., 1990; Paige, Reid, Allen, & Newton, 1990; Shalev, Orr, Peri, Schreiber, & Pitman, 1992; Orr, Lasko, Shalev, & Pitman, 1995). This tendency to interpret ambiguous events as threatening and to respond with heightened physiological arousal distracts attention from current activities. The distraction interrupts the development of more adaptive information processing structures for dealing with normal, non-threatening circumstances,

> *. . . threat arousal inhibits the operation of other information-processing modes or schemata, thereby preventing their operation and further narrowing the attentional focus on threat-related stimuli (Chemtob et al., 1988, p. 266).*

In addition to these cognitive models of PTSD, there is a substantial literature on biological models of PTSD (see overview in Pitman, 1997). One of the most influential neuropsychology theories was Kolb's (1987) explanation for intrusive memories and associated arousal in PTSD. He started from a two-factor learning theory that PTSD results from both classical conditioning of extreme emotional responses to traumatic stimuli (i.e., fear, terror, anger, rage, sadness, guilt, and indignation) and operant conditioning of emotional numbing, withdrawal, and avoidance of traumatic stimuli. Kolb (1987) adopted a neuropsychological explanation of information processing deficits in PTSD, when he proposed that PTSD results from excessive traumatic stimulation that overwhelms efficient information processing.

> *Such stimulus overload occurs when the ... capacity to process information signaling threat to life overwhelms the cortical ... processes concerned with perceptual discrimination and effective adaptive responses for survival (Kolb, 1987, p. 993).*

Excessive threatening stimulation sensitizes neuronal circuits that are responsive to threat, including structures in the "temporal-amygdaloid complex concerned with agonistic behavior", which may "lead to depression [or atrophy] of those synaptic processes which permit habituation and thus discriminative perception and learning" (Kolb, 1987, p. 993). As a result of this initial sensitization and a diminished capacity for discrimination, sensitivity to threatening stimuli generalizes, via a process of higher order conditioning, from an initial traumatic experience to a variety of similar threatening situations (Kolb, 1987). Furthermore, Kolb (1987) proposes that this generalized sensitivity to threatening situations perpetuates agonistic affect, such that limbic activity disrupts frontal executive systems; in particular, the frontal systems that inhibit the locus ceruleus and its noradrenergic innervations of diverse cortical and subcortical structures. A possible increase in cortical and subcortical noradrenergic

activation further enhances the sensitization and activation of the trauma schema (Kolb, 1987). As a result,

> *in the face of perceived threats there occurs excessive sympathetic arousal - including neuroendocrine disturbances as well as behavioral expressions of rage and irritability and repetitive cortical reactivation of memories related to the traumatic events. The latter are projected in the daytime as intrusive thoughts and at nighttime in the recurrent traumatic nightmares of PTSD ... (Kolb, 1987, p. 994).*

Thus, Kolb (1987) proposed that PTSD reflects a vicious positive feedback loop of threat related stress and hyperactivity. Firstly, a traumatic experience engages the fight or flight stress response that overwhelms the cognitive system and promotes sensitivity to threatening stimulation that continues to disrupt efficient information processing beyond the immediate trauma circumstance. Secondly, this threat sensitivity engages central and peripheral adrenergic hyperactivity and feedback from this stress response activates and reinforces the threat schema, so a positive feedback loop is established (see also Burges-Watson, Hoffman & Wilson, 1988). From an evolutionary perspective, it is adaptive to respond to ambiguous or threat related stimuli with intense and rapid stress reactions in dangerous situations, but the persistence of those reactions into more generalized, neutral circumstances is inappropriate and can be debilitating, which would appear to occur in PTSD.

Similarly, Everly (1989, 1993) proposed that PTSD comprises a psychological sensitivity to threat and a hyperactive stress response system (see also Weil, 1974; cited in Everly, 1993, p. 273). According to Everly (1993), the cognitive sensitivity to threat involves frontal and cingulate cortex, which activate affective and somatic stress responses in limbic structures, the sympathetic nervous system, and neuroendocrine activity in the hypothalamic-pituitary-adrenal system. Furthermore, this system comprises a positive feedback loop, such that:

> *. . . affective discharge from the limbic brain sends neural impulses in two simultaneous directions: 1) to neocortical targets, and 2) to the skeletal musculature . . . . The neocortical centers then send impulses back to the limbic areas, thus sustaining affective arousal. At the same time, proprioceptive impulses from the skeletal musculature ascend via the reticular formation and further stimulate limbic and neocortical targets. This complex positive feedback loop serves to sustain and intensify [threat related arousal] (Gellhorn, 1965, 1967; cited in Everly, 1993, p. 273).*

This hyperarousal may have long-term neurological consequences; intense or protracted stimulation can produce various structural and functional changes in networks of the limbic system (Weil, 1974; Post, 1985, 1986, 1992; cited in Everly, 1993, p. 273-274; see also Bremner et al., 1995). Everly (1989) proposes that tonic or phasic hyperactivity of the noradrenergic system in the septo-hippocampal-amygdaloid formation explains many facets of the phenomenology of PTSD, including heightened startle responses and autonomic hyperactivity, emotional lability, irritability, fear, guilt, aggression, and intrusions such as flashbacks and nightmares. The noradrenergic system of the septo-hippocampal complex is involved in both the integration of novel or aversive stimulus information and the concomitant activation of amygdala and hypothalamic-pituitary responses to threat (Gray, 1982a,b). Also, activity in the septo-hippocampal-amygdaloid network is involved in memory and panic or fear reactions (Reiman et al., 1986; Gloor, 1986; Post, 1986; Seifert, 1983; cited in Everly, 1989, p. 316). Moreover, noradrenergic activation of the septo-hippocampal-amygdaloid system both inhibits its accommodation or habituation (Madison & Nicoll, 1982; cited in Everly, 1989, p. 316) and sensitizes it and facilitates its response to further novel or aversive stimuli (Gray, 1982a,b).

Recently, van der Kolk (1997) has also professed the role of limbic and cortical systems in traumatic cognitions. Following Janet, he proposes that traumatic cognitions are dissociated fragments of sensory and emotional experiences that are not well

integrated with other neutral episodic memories and thereby prevent the development of trauma narratives (which could facilitate recovery). Furthermore, this fragmentation is a symptom of abnormal functions of neural systems involved in the evaluation and integration of experience. Several neural networks are involved, including (a) the parietal cortex in integration of multimodal sensory information, (b) the hippocampus in integration of episodic memory, (c) the cingulate as a modulator of relevant information processing, enhancing relevant and inhibiting irrelevant information, and (d) the prefrontal cortex in executive control of various integrative processes (van der Kolk, 1997; see also McFarlane et al., 2002).

The following discussion, together with introductory material in the results chapters, gives further insight into these theories, with consideration of cognitive neuroscience research into limbic and cortical systems engaged in attention and memory processes. It can be seen that the relations between limbic and cortical systems are important for stimulus evaluation, working memory and episodic memory, as well as associated emotional and visceral states.

1.2.1 Limbic Systems and Cortical Networks: Dysfunctions in PTSD

Recent work demonstrates abnormal hippocampal anatomy in PTSD, which has important implications for cognitive functions in PTSD. Functional neuroimaging of the hippocampus demonstrates its role in novel stimulus evaluation, episodic memory, and the spatio-temporal coherence of experience. Abnormal hippocampal functions may explain dissociative states in PTSD. Also, evidence indicates abnormal amygdala and anterior cingulate responses in PTSD, which contribute to emotional lability, especially exaggerated fear and stress responses.

1.2.1.1 Smaller Hippocampal Volume in PTSD

Several studies have now employed high-resolution magnetic resonance imaging (MRI) to measure the volume of the hippocampus. The studies report 5-30% reduced hippocampal volume in PTSD, with associated deficits in verbal memory (Bremner et al., 1995, 1997; Gurvitis et al., 1996; Stein, Hanna, Koverola, Torchia & McClarty, 1997; Bonne et al., 2001; Gilbertson et al., 2002). These studies involve careful anatomical judgment during the selection and measurement of hippocampal regions, so it is important that they involve blinded research designs (Bonne et al., 2001). This degree of hippocampal atrophy is smaller in PTSD than amnesia. For example, Press, Amaral, and Squire (1989) report a 49% reduction of hippocampal volume in amnesic patients (with normal parahippocampal volumes). These patients showed severe deficits of verbal and non-verbal memory, while performing normally on other tasks (Press et al., 1989). Nevertheless, the functional significance of the hippocampal abnormality in PTSD has prompted careful examination of this structure.

Bremner et al. (1995) found an 8% reduction of right hippocampal volume in Vietnam veterans with PTSD, which was associated with deficits in verbal short-term memory (see also Bremner, 2001). Gurvitis et al. (1996) report bilateral hippocampus reduction in combat PTSD, after controlling for age and whole brain volume. The decrease was greater in left (26%) than right (22%) hippocampus, especially after controlling for alcohol abuse and combat exposure. Hippocampal volume was negatively correlated with both combat exposure and PTSD symptom severity. Furthermore, hippocampal volume was positively correlated with several measures of attention and memory (digit span, arithmetic [WAIS-R], attention index [Wechsler memory scale], and delayed recall errors [Benton visual retention test]).

Several studies now demonstrate smaller hippocampus in adults with a history of childhood abuse (Bremner et al., 1997; Stein et al., 1997). Bremner et al. (1997) found

a 12% smaller left hippocampal volume in adult survivors of chronic childhood abuse (7 to 15 years of physical, sexual or emotional abuse), with 10% of this effect solely related to PTSD diagnosis (after sex, age, education or alcohol abuse were controlled). In a similar population, Stein et al. (1997) found a 5% smaller left hippocampus in women survivors of severe childhood sexual abuse. Bremner et al. (1997) found no correlations between left hippocampal volume and verbal memory impairments (immediate and delayed recall and retention), trauma onset or duration, years since trauma cessation, or PTSD symptom severity (cf., Gurvitis et al., 1996). Bremner et al. (1997) propose that trauma early in life may damage hippocampal structures and neural plasticity could recover the integrity of verbal memory processes. In this regard, they propose that some functions of the hippocampus may have shifted to the left temporal lobe, which was larger in patients (Bremner et al., 1997). However, it is also possible that larger left temporal lobes could be related to better visual performance, which might be an adaptation to a loss of verbal capacity (Bremner et al., 1997).

There are concerns that hippocampal volume in chronic PTSD may result from substance abuse or other confounds and it is not clear whether smaller hippocampal volumes precede or follow a traumatic experience (see Bremner, 2001; Pitman, 2001). One longitudinal study has reported no decrease in hippocampal volume between 1 week and 6 months after trauma (Bonne et al., 2001). This study had tight controls over substance abuse and it employed a blinded measurement design, whereby the persons measuring hippocampal volume were blind to both the group and time status of the data. However, this study only investigated subjects older than 20 years, after which normal development of the hippocampus and other limbic structures is complete, whereas some previous studies have investigated patients who experienced trauma during childhood or early adulthood. Nevertheless, this study identified abnormal attention and executive functions, despite a lack of clear evidence for hippocampal atrophy, suggesting that

executive networks are already dysfunctional in the first 6 months of PTSD (Bonne et al., 2001). The possible conclusions are: (a) there is no hippocampal atrophy and previous findings are confounded, or (b) there is atrophy, but it may take longer than 6 months to appear, so atrophy is only apparent in chronic patients, or (c) a smaller hippocampus might predispose some people to PTSD and especially chronic PTSD (see Pitman, 2001).

With regard to (c), another recent study has investigated whether smaller hippocampal volume may indicate a susceptibility to PTSD. Gilbertson et al. (2002) compared combat veterans with and without chronic PTSD, together with their monozygotic twins who had no combat exposure. They found 10% smaller hippocampal volume in the PTSD twin pairs and there was a significant negative relationship between hippocampal volume and the severity of PTSD in the combat veterans with PTSD ($r = -0.64$) and their twin brothers ($r = -0.70$). The hippocampal volume effect remained significant after controlling for whole brain volume, age, combat exposure, and non-combat trauma incidents (including childhood physical or sexual abuse). There were no significant differences in total brain volume or amygdala volume. They conclude that smaller hippocampus could be a trait indicator of the likely development of PTSD after traumatic exposure (Gilbertson et al., 2002). However, smaller hippocampal volume was concentrated in the severe PTSD cases. The group differences in hippocampal volume only apply to severe PTSD after combat exposure (CAPS > 65, based on a subsample of 24 from 34 combat PTSD cases). Also, the combat veterans with PTSD had a history of more alcohol abuse than any other group in the study, so the results could be confounded by alcohol abuse. Thus, this study may provide evidence that combat exposure is not a necessary condition for hippocampal atrophy, but further longitudinal studies are required to confirm this conclusion (Gilbertson et al., 2002; see also Sapolsky, 2002).

The findings of abnormal neuroanatomy in PTSD may be specific to hippocampal volume, rather than a general or diffuse neurological abnormality. Bremner et al. (1997) noted no significant differences in several regions, including caudate and amygdala. Similarly, Gurvitis et al. (1996) found no differences in intracranial cavity, whole brain, ventricles, ventricle:brain ratio, or amygdala (although, the right amygdala was larger in patients than controls, which approached significance at .07). Likewise, Gilbertson et al. (2002) found no differences in whole brain or amygdala volume.

However, there are now two reports of extra-hippocampal abnormality in PTSD. The first study indicated focal white matter lesions in only 8 of 42 combat related PTSD patients (Canive et al., 1997). The lesions were in periventricular regions or near the white/gray cortical junctions. The lesions were not associated with symptom severity or comorbid depression or alcohol abuse. Another study involved more comprehensive cortical parcellation in nurses with combat exposure (Rauch et al., 2003). Although whole cortical volume was normal, this study clearly identified smaller cortical volume in the anterior cingulate and subcallosal cortex (some near significant decreases were identified in the angular gyrus, inferior occipito-temporal gyrus and the supplementary motor cortex; Rauch et al., 2003). Thus, PTSD symptoms have been related to abnormalities in several regions of the central nervous system, but primarily the hippocampus and anterior cingulate.

1.2.1.2 Hippocampal Physiology and Integrity

An explanation for abnormal hippocampal volume in PTSD depends on the physiology of cortisol in the neuroendocrine system (e.g., Pitman, 1989). The CA3 region of the hippocampus is a target for glucocorticoids in the brain, as it plays a role in regulating the hypothalamic-pituitary-adrenocortical (HPA) response to stress. Under stressful conditions, glucocorticoid levels usually increase, which is detected in the hippocampus (among other locations of the HPA axis), effecting negative feedback

controls. The hippocampus inhibits discharge of corticotrophin releasing factor from the hypothalamus, thereby, diminishing further cortisol responses to stress (Murburg, 1997). However, chronic, elevated levels of glucocorticoids can induce dendritic loss and atrophy in the hippocampus (Watanabe, Gould, & McEwen, 1992; Sapolsky, 1996; McEwen & Magarinos, 1997; McEwen, 1999, 2001; see also Bremner, 2001; Yehuda, 2001). Glucocorticoids can interfere with the reuptake of glutamate from the synaptic cleft, resulting in greater activation of post-synaptic N-methyl-D-aspartate (NMDA) receptors and the consequent excess of intracellular calcium. Intracellular calcium has a variety of potentially dangerous metabolic activities, but it is usually efficiently metabolized. An excess of glutamate and NMDA activation counteracts this process of calcium extraction and cellular repair. Furthermore, glucocorticoids interfere with glucose metabolism, which is required for calcium extraction and cellular repairs. Thus, excessive activation of NMDA receptors can lead to cellular breakdown. This physiology is related to several possible explanations for hippocampal anatomy in PTSD, including (a) hippocampal dendritic pruning, (b) cellular atrophy or (c) inhibition of neurogenesis (see Bremner, 2001; McEwen, 2001).

However, studies of glucocorticoid levels immediately after exposure to trauma indicate that decreased cortisol predicts development of PTSD, whereas increased cortisol predicts onset of depression (see McFarlane, 1997; Yehuda, 2001). This evidence is inconsistent with the hippocampal atrophy hypothesis of elevated cortisol levels in PTSD. However, there is another possible explanation for hippocampal atrophy that does not depend on elevated cortisol levels. This explanation refers to evidence of greater glucocorticoid receptor density and sensitivity in the HPA feedback circuits among people who develop PTSD, suggesting an abnormal sensitivity to stress and more negative feedback on the HPA endocrine response (Yehuda, 2001). It is not yet clear whether greater receptor sensitivity or density actually facilitates abnormal

hippocampal anatomy, although this explanation could be consistent with observations of decreased hippocampal volume.

Although MRI evidence implicates changes in hippocampal anatomy, these changes are not necessarily a clear indication of pharmacological disturbance. If the hippocampal elements of the HPA feedback circuits are disturbed, the mechanisms for feedback control of stress are disrupted, which may lead to decreased habituation of fear and stress responses. The hippocampus plays a role in contextual stimulus evaluation and fear conditioning, so if the circuits of the hippocampus are disrupted, learning and memory processes are impaired, which is observed in PTSD. A possible mechanism for this pharmacological disruption involves acetylcholine, as evidence indicates that acetylcholine synapses in the hippocampus are involved in contextual fear conditioning; that is, acetylcholine antagonists interfere with fear conditioning to context (e.g., Gale, Anagnostaras & Fanselow, 2001). A possible explanation is that acetylcholine is important for hippocampal theta rhythms and interference with this activity impairs the capacity of the hippocampus to integrate sensory information about context (Gale et al., 2001; also discussed further below). Furthermore, there may be important interactions between acetylcholine and NMDA receptors, which are implicated in hippocampal dendritic pruning, atrophy and neurogenesis processes (see McEwen, 1999, 2001; Gale et al., 2001; Bremner, 2001; Yehuda, 2001). Also, the involvement of NMDA and serotonin has been demonstrated by inhibition of stress induced deterioration or atrophy with application of tianeptine and phenytoin (Watanabe, Gould, Cameron, Daniels & McEwen, 1992; Watanabe, Gould, Daniels, Cameron & McEwen, 1992; McEwen, 1999). The effects on hippocampal dendrites related to glucocorticoids and NMDA physiology can be observed after 14 days, suggesting a long-term response or adaptation process (McEwen, 2001). In fact, evidence suggests that acute stress can induce long-term modulation of cholinergic gene expression; acute stress can promote a

short-term increase, but a long-term depression in acetylcholine activity (Kaufer et al., 1998). Evidence indicates that cholinergic systems play an important role in attention, learning and memory; decreases in cholinergic activity in hippocampal regions increase susceptibility to novelty detection and distraction (see Baxter & Chiba, 1999; cf. Murburg, 1997). Also, some evidence implicates abnormal noradrenergic activity in PTSD, with one positron emission tomography (PET) study of yohimbine, an adrenergic stimulant, demonstrating abnormal activity in hippocampus, as well as prefrontal, orbitofrontal, parietal and temporal cortex (Bremner, Innis et al., 1997). Perhaps these cellular processes provide an explanation for the impact of trauma on contextual stimulus evaluation and learning in PTSD, which appears to consist of overgeneralization from one context to many contexts and failure to habituate. Note that such physiological disturbances need not be associated with any abnormality of hippocampal volume; even normal levels of glucocorticoids can induce dendritic remodeling (McEwen, 2001; cf. Yehuda, 2001), or the effects of stress may be related to neurotransmission adaptations and gene expression (see discussions of sensitization and kindling; e.g., Post, 1992; Post et al., 1997; see also Pitman et al., 2002; Vaiva et al., 2003). Nevertheless, it is a disturbance of hippocampal functions that play an important role in the response to trauma in PTSD.

Whether hippocampal volume is diminished in chronic PTSD as a result of genetic inheritance, prenatal development or exposure to trauma, it is clear that the integrity of this structure plays an important role in PTSD. The following discussion will outline the role of the hippocampus and associated networks in cognition.

1.2.1.3 Integrating New Experience with Memory: Interactions of the Hippocampus, Parahippocampal and Associative Cortex

Given evidence of hippocampal abnormalities in PTSD it is important to understand the role of the hippocampus in cognition – what functions does it perform and how is it related to other subcortical and cortical systems?

The anterior CA1 region of the hippocampus receives inputs from the temporal, parietal, and olfactory cortices (Eichenbaum & Otto, 1993). Coherent interactions of temporal and parietal cortex serve to integrate object perceptions and spatial orientation with motor guidance (Knudsen & Brainard, 1995; Dolan et al., 1997; Rodriguez et al., 1999; von Stein, Rappelsberger, Sarnthein & Petsche, 1999). Activity from these temporal and parietal regions has been found to project directly to CA1 pyramidal cells of the hippocampus, suggesting that the hippocampus directly receives multimodal representations of spatio-temporal object information (Rockland & van Hoesen, 1999). Furthermore, there are connections between the hippocampus and the executive systems of the parietal and prefrontal cortices, which facilitate integration of sensory representations with movement intentions (Eichenbaum & Otto, 1993). Thus, the hippocampus and parahippocampal cortex lies within a distributed network of higher-order perceptual and motor systems.

It is generally accepted that the hippocampus is involved in the generation and recollection of episodic memories. This conclusion is supported by evidence of hippocampal atrophy in Alzheimer's disease and the classic case of HM (Corkin, 2002), which demonstrate that hippocampal lesions lead to failures in consolidation of new memories (cf. role of amygdala, McGaugh, 2002).

Episodic memory encoding is selective; the information stored is mostly new experiences that contribute to understanding the world. There is evidence that the role of the hippocampus is to detect or extract the significant information for further memory

consolidation from the less important, repetitive material that is already stored. The hippocampus is involved in the ongoing comparison of cognitive expectations against sensory inputs for the purpose of maintaining accurate representation of the environment (e.g., Strange, Fletcher, Henson, Friston & Dolan, 1999; Strange & Dolan, 2001; Lisman & Otmakhova, 2001; Vinogradova, 2001; see also Gray, 1982a,b, 1988). In performing this process, the hippocampus has access to higher order or supramodal episodic representations that contain both stimulus and response information over time (Eichenbaum & Otto, 1993; Martin, Wiggs, Ungerleider & Haxby, 1996; Stern, Sherman, Kirchhoff & Hasselmo, 2001; Vinogradova, 2001).

Two important aspects of cognition influence the effectiveness of memory encoding: (a) undivided attention and (b) encoding the meaning rather than stimulus properties (Rugg, 1998). The first of these, attention, is either consciously directed or engaged by novelty. Once attention is directed to a percept, it is likely that evaluation processes translate the simple sensory information into meaningful representations, which facilitate encoding (Rugg, 1998). Thus, novelty is one important determinant of what is encoded into episodic memory (Tulving & Kroll, 1995).

The hippocampus is a key structure in the detection of novelty or familiarity. Evidence indicates that activation along the anterior-posterior axis of the hippocampus reflects a distribution of stimulus novelty to familiarity. For instance, Strange et al. (1999) report that anterior hippocampal regions respond to perceptual novelty, whereas posterior regions respond to stimuli that have response related familiarity. They propose that the anterior hippocampus registers mismatches of current stimulus information against an expected or predictive representation. When mismatches are identified and they have behavioral significance, greater attention and familiarity with the information engages posterior hippocampal regions. Furthermore, the activity along this hippocampal axis for the detection of novelty or familiarity may help to explain

anterograde or retrograde amnesia. Strange et al. (1999) postulate that damage to the anterior hippocampus impairs novelty detection and episodic memory consolidation, which explains anterograde amnesia. Conversely, damage of the posterior hippocampus impairs recall of past experience, which may explain retrograde amnesia (Strange et al., 1999; see also Lisman & Otmakhova, 2001; Stern et al., 2001; Strange & Dolan, 2001; Vinogradova, 2001).

Although hippocampal and parahippocampal regions are involved in detection of novelty, evidence indicates that complex encoding strategies engage cortical regions. The reports of Wagner et al. (1998) and Brewer, Zhao, Desmond, Glover and Gabrieli (1998) indicate that left prefrontal and parahippocampal regions are active during encoding and consolidation in an incidental memory task. Their task materials did not involve novelty and did not elicit activation in the hippocampus proper. It may be that the hippocampus is not directly involved in encoding or consolidation, but merely detects novelty and thereby initiates more complex evaluation, encoding, and consolidation, which involve cortical processing. This interpretation is supported by a dissociation of frontal and hippocampal functions reported by Dolan and Fletcher (1997; see also Grunwald, Lehnertz, Heinze, Helmstaedter & Elger, 1998; Stern et al., 2001). They found that the left prefrontal cortex is engaged by changes in the content of linguistic category-exemplar encoding processes, implicating this brain area in the controlled transformation of auditory-verbal stimuli into meaningful information. On the other hand, left medial temporal areas, including the hippocampus, were responsive to contextual novelty. When the physical properties of auditory-verbal stimuli were familiar, but the novelty of the stimuli was related to the encoded associations of the verbal information, the medial temporal structures responded to the associative or contextual novelty of the material (Dolan & Fletcher, 1997). The hippocampal detection of novelty serves to initiate the integration of new information in working

memory, which engages frontal executive processes that may alter the stimulus encoding and further integrate the information with response plans.

The process of contextual novelty detection involves identification of objects and events in spatio-temporal relationships. The multimodal inputs generated by the neocortex contain the highest level of representation of the stimulus environment and movement intentions (Eichenbaum & Otto, 1993). Many reports indicate that hippocampal cells respond to various spatial and object properties of the stimulus environment, as well as the position or motor intentions of the organism in the environment (see Eichenbaum & Otto, 1993). For instance, some cells of anterior hippocampal regions, CA1 and CA3, are involved in allocentric spatial mapping of objects into episodic memories (i.e., independent of the position or orientation of the observer), but these cells interact with and rely on neighboring cells that spatially map head position/orientation and relative position of the body with regard to these objects (Georges-Francois, Rolls & Robertson, 1999; Rolls, 1996). In general, the hippocampus is responsive to the higher order contextual relevance or significance of stimuli.

The contextual or episodic processes of the hippocampus modify multimodal representations in two important ways (Eichenbaum, 1997). Firstly, it assists the association of an object or event with its current or previous context. Secondly, it can differentiate an object or event from its context, which is important for perceptual constancy. For instance, after initially meeting a person in one context, we need to be able to recognize them again a day later while they are wearing different clothes in a different place. This requires considerable extraction of person specific percepts from a potentially vast array of information. Given spatial inputs and integration functions of the hippocampus and the importance of spatial orientation to survival, it would seem that hippocampal inputs into episodic memories contribute primarily spatio-temporal

orientation, which can be important for evaluation of the novelty or familiarity of an object or event in a location.

Furthermore, Eichenbaum (1997) proposes that the hippocampal inputs into associative memories can influence the latter retrieval cues for the memories (see also Nadel & Moscovitch, 1998). The quality or amount of episodic information and the manner of integration of that information into the associative memory networks will affect what type and how many cues can elicit memories and how much of the memories they elicit. For instance, an interleaved encoding of episodic with various multimodal or semantic representations can better facilitate retrieval of the whole episode and it's specific representations (Eichenbaum, 1997). There is some evidence of functional lateralisation in the hippocampus, with the left hippocampus more responsive to verbal or linguistic representations (Wagner et al., 1998), whereas bilateral or right hippocampus is more responsive to pictorial or object representations (Brewer et al., 1998). Thus, the hippocampus is integrated into the general hemispheric lateralisation of function.

It is interesting to note that while the hippocampus may contribute to the episodic or contextual framework for multimodal or semantic representations, the memories may be encoded in the interactions of the parahippocampal and association cortices (Eichenbaum, 1997; see also van Hoesen, 1982; Grunwald et al., 1998; Nadel & Moscovitch, 1998; Rockland & van Hoesen, 1999). Several studies indicate that even in the absence of the hippocampus, semantic memories can be encoded and consolidated by interactions of parahippocampal and associative cortex (Eichenbaum, 1997; Desimone, 1996; Brewer et al., 1998; Wagner et al., 1998). Various studies report that such memories are established in animals and humans with hippocampal damage, but not so with parahippocampal damage (Eichenbaum, 1997). In contrast, evidence that the hippocampus provides contextual or episodic information arises from

deficits in locating objects or faces in their spatial context among individuals with developmental hippocampal pathology (Vargha-Khadem et al., 1997). Thus, while the hippocampus is important for comparisons, which indicate novelty or familiarity, it may not be directly involved in encoding and consolidation, which involves parahippocampal and cortical networks.

In general, the interactions of the cortex and parahippocampal structures serve to integrate and hold multimodal and semantic representations, while the hippocampus serves as a comparator and organizer of these representations (Eichenbaum, Schoenbaum, Young & Bunsey, 1996; Goldman-Rakic, 1996; Dusek & Eichenbaum, 1997; Rockland & van Hoesen, 1999; Lisman & Otmakhova, 2001; Vinogradova, 2001). This process of comparison involves iterative information processing, which involves complex interactions between the hippocampus and the parahippocampal regions. Iijima et al. (1996) propose that reverberating circuits in the entorhinal cortex (EC) and cyclic interactions between the EC and hippocampus play an important role in holding information and selectively gating it into hippocampal circuits. The superficial layers of the EC receive multimodal input from association cortices. The EC can selectively gate this information into a spatial and temporal integration in reverberating circuits that hold the information. Furthermore, the EC is a major cortical input into the hippocampus and it can selectively gate the information from its reverberating circuits into the hippocampus. The hippocampus can, in turn, process this information and return inputs from CA1 and the subiculum into the deep layers of the EC, where it can reintegrate into the EC circuits or feedback into the association cortex. Iijima et al. (1996) demonstrated, in real-time, that the reverb circuit of the rat EC oscillates at about 5 Hz, which included activation and feedback in the hippocampus (see also Fernandez et al., 1999).

The outcome of novelty comparison processes may be the integration and consolidation of new information into complex memory structures (see, Nadel & Moscovitch, 1998; see also LeDoux, 2002). Memory consolidation is generally considered a process of long-term potentiation (LTP) of nerve cell membranes. There are a variety of models proposed to explain the neurochemistry of LTP (see Bailey, Bartsch & Kandel, 1996; Lisman & Fallon, 1999). Several models of early phases of LTP implicate membrane proteins and second messenger systems in positive feedback processes designed to maintain an active membrane state (Lisman & Fallon, 1999). Models of later phases of LTP implicate gene expression in stable changes of membrane or synapse structure and functions (Lisman & Fallon, 1999). Bear (1996) reports that LTP and long-term depression occurs in both the hippocampus and the cerebral cortex, which supports a possible role of interactions between these regions in consolidating new memories (see also Rockland & van Hoesen, 1999).

1.2.1.4 Emotional Valence: Limbic Systems and Executive Attention Systems

The hippocampus not only signals novelty in the process of evaluating new information and associated episodic memories; it also acts as a warning system for behavior when significant mismatches between expectations and sensation occur. This alerting system is what Gray (1982a,b, 1988) has called the behavioral inhibition system (BIS), which plays an important part in anxiety (see also, Derryberry & Tucker, 1992; Nadel & Jacobs, 1996, 1998). The BIS is activated by unpredictable stimuli that require reappraisal of appropriate action plans. The anterior hippocampus is involved in registration of mismatches between expectations, based on recent experience, and current events (Gray, 1995; Dusek & Eichenbaum, 1997; Grunwald et al., 1998; Strange et al., 1999; Vinogradova, 2001).

An important part of stimulus evaluation is the determination of the emotional valence of any sudden changes or unusual circumstances. In general, novel or

unexpected events can be appealing or aversive, and it can be critical to act swiftly if a novel event threatens physical or emotional harm. The anatomical connectivity of the amygdala provides for fast processing of the emotional valence of events, as it receives projections from various subcortical and cortical somatic, sensory and associative regions (Derryberry & Tucker, 1992; Rolls, 1995, 2000; LeDoux, 2002). LeDoux (1990, 1995, 2002) has shown that the amygdala plays a critical role in the generation of fear and anger, but it also plays a role in memory consolidation for aversive events (McGaugh, 2002; McGaugh, McIntyre & Power, 2002; see also Pitman et al., 2002; Vaiva et al., 2003). In conjunction with the hippocampus and cortical systems, the amygdala facilitates emotional evaluation of new information; it can identify events that are likely to cause harm and initiate a cascade of responses designed to prepare the body for fight or flight responses. Also, the amygdala is implicated in modulation of cortical processing, including affective and episodic memory systems (e.g., Derryberry & Tucker, 1992; Rolls, 1995, 2000; McGaugh, 2002; McGaugh et al., 2002; LeDoux, 2002).

The signals from limbic system circuits have a close relationship with attention systems, including the visual orienting and sustained attention networks of the parietal and the anterior cingulate cortex (see Posner & Raichle, 1994; see also Derryberry & Tucker, 1992; Gray 1995; Rolls, 1995, 2000; McGaugh, 2002). There are important functional connections between various subcortical, limbic and cortical systems for stimulus evaluation and orienting attention, which include connections between the anterior thalamus, amygdala (especially the lateral nucleus), hippocampus (especially the subiculum), and cortical systems (including the entorhinal cortex, multimodal sensory systems in parietal cortex, and the executive systems of the frontal cortex, especially the anterior cingulate; see Posner & Raichle, 1994; Gray, 1995; Rolls, 1995, 2000; LeDoux, 2002, McGaugh, 2002). If the attention system is interrupted by a novel

or threatening event, the anterior cingulate may either inhibit the distraction to continue with ongoing activity or it may halt current activity to divert attention resources to more careful evaluation of the new environment. The anterior cingulate has close connections with medial and orbital frontal systems involved in emotional evaluation and also the premotor systems that can be engaged to stop and redirect ongoing actions. In general, the cortical system serves to coordinate actions and develop adaptive action patterns that are responsive to environmental conditions and appetitive and emotional states (see Derryberry & Tucker, 1992; Rolls, 1995, 2000).

1.2.1.5 Implications for PTSD

Dysfunction of the hippocampus and coupled parahippocampal networks in PTSD can affect the ability to accurately evaluate and incorporate new information into multimodal sensory and working memory representations. Dysfunction of hippocampal and parahippocampal processes in PTSD does not rest on anatomical abnormality. It is possible that neurotransmitter physiology increases the sensitivity of hippocampus novelty detection, with associated disruption of attention and episodic memory systems. The failure to assimilate new information into episodic memory will impair the creation and adaptation of cognitive models of the environment, which are used to predict outcomes of behavior. Any discordance between a cognitive model and current experience can generate mismatch activity in the hippocampus and activate novelty attention processes. Furthermore, the hippocampal mismatch activity and associated orientation of attention may be associated with greater fear or threat appraisal, involving activity of the amygdala (although the reciprocal connections among limbic systems may preclude simplistic causal modeling; cf. Villarreal & King, 2001). Although fear and stress responses are normally inhibited or habituate, this is not the case in PTSD, leading to hyperarousal, hypervigilance and eventually to cognitive, emotional, and endocrine exhaustion. The prevention of this exhaustion can involve intense avoidance

strategies. Thus, abnormal episodic memory systems, coupled with avoidance, could explain why PTSD patients are less able to accommodate new information after their trauma and the most recent traumatic memories that were consolidated continue to affect perception and expectations. Their cognitive, affective and somatic responses become caught in trauma.

When attention systems are easily distracted by novel events, coupled with threat appraisal processes that are engaged by ambiguous information, patients are more susceptible to stress responses. Furthermore, with greater affective responses to trauma or threat stimuli, that information is more likely to be incorporated into episodic memory. Conversely, neutral information may not gain adequate attention, so it is less likely to be fully evaluated and integrated into cognitive structures. The attention system becomes diverted away from neutral information toward novelty and threat. This can have diverse implications, including failure of top-down modulation of early sensory discrimination, which is a fundamental mechanism of tuning the sensory system for adaptive information processing.

The relationship of emotion and cognition in PTSD is complex, given that it arises from intricate and extensive limbic and cortical networks. However, it is likely that abnormal hippocampal functions contribute to poor stimulus evaluation (especially contextual evaluation), dissociation of episodic memory, excessive novelty detection and behavioral inhibition, plus general disruption of executive cognition. The cognitive disorder involves impaired integration of new information into neutral schemata, which is related to deficient concentration and attention strategies. It thereby impairs the ability to detect, evaluate, and consolidate knowledge about the regularities in various, especially complex, stimulus arrays. The failure to integrate new information into cognitive structures creates reliance on previous learning and less pressure to replace traumatic content with new experiences. The sensitivity to novel or ambiguous events,

coupled with threat appraisal, activate trauma schemata, thereby generating intrusive states. In this manner, given deficits in contextual evaluation, PTSD patients could generalize from a specific trauma incident to various contexts. The following review of cognitive, neuropsychological and physiological evidence supports the theory that PTSD comprises sensitivity to trauma and a concomitant failure to assimilate neutral information.

1.3 Research Evidence: Trauma Sensitivity

This section is a short review of trauma information processing and associated psychophysiology in PTSD (see also Buckley et al., 2000; Villarreal & King, 2001). The research work clearly demonstrates greater attention and stress responses for trauma information in PTSD. This section can be compared with the following section, which reviews studies demonstrating neutral information processing deficits in PTSD.

1.3.1 Cognitive Psychology

Studies of a modified Stroop task demonstrate greater attention for words associated with traumatic incidents in PTSD patients than trauma survivors and normal controls (Trandel & McNally, 1987; McNally, Kaspi, Riemann, & Zeitlin, 1990; Foa, Feske, Murdoch, Kozak, & McCarthy, 1991; Cassiday, McNally, & Zeitlin, 1992; Thrasher, Dalgleish, & Yule, 1994; Bryant & Harvey, 1995). This sensitivity is positively associated with the severity of PTSD symptoms, especially traumatic intrusions (McNally et al., 1990; Cassiday et al., 1992). Furthermore, there is residual sensitivity after recovery from PTSD; so although symptoms abate, the underlying trauma schema remains coherent (Cassiday et al., 1992).

Several studies also demonstrate memory biases for traumatic information. Zeitlin and McNally (1991) found that combat veterans with PTSD have good implicit memory for combat information, but poor for neutral or positive information, especially

life events after their combat exposure. This implicit bias was positively associated with the severity of PTSD and it could reflect a chronic potentiation of elaborate and stable combat memories (Zeitlin & McNally, 1991). Also, veterans with PTSD have difficulty recalling any specific emotional experiences, but those recalled are often negative or traumatic states (McNally, Litz, Prassas, Shin, & Weathers, 1994; McNally, Lasko, Macklin, & Pitman, 1995).

1.3.2 Cognitive Psychophysiology

Event-related brain activity has been employed to investigate various aspects of cognition (e.g., Kutas & Hillyard, 1984). Cognitive ERP studies provide biological indices of information processing that confirm the trauma sensitivity in PTSD. These biological indices provide insight into the temporal dynamics of cognitive processes that are activated by trauma in PTSD.

Combat veterans with PTSD demonstrate enhanced ERP responses to traumatic images. Combat veterans with PTSD demonstrate larger visual N1 and P3 amplitudes and shorter P3 latency for non-target, rare distracting combat pictures (Attias, Bleich, & Gilat, 1996; Attias, Bleich, Furman, & Zinger, 1996; see also Shalev et al, 1988; Shalev, Orr & Pitman, 1993). An increase in N1 amplitude reflects an early, automatic allocation of attention to identification and discrimination of the physical attributes of stimulus information; in this case, the results indicate that PTSD patients automatically orient to traumatic images (Attias, Bleich, & Gilat, 1996; Attias, Bleich, Furman, & Zinger, 1996). An increase in P3 amplitude in response to combat pictures indicates greater conscious attention to the subjective significance or meaning of the traumatic images, which depends on prior exposure and sensitivity to their traumatic content (Attias, Bleich, & Gilat, 1996; Attias, Bleich, Furman, & Zinger, 1996). Also, the latency of the P3 in response to traumatic images was positively associated with the

frequency of traumatic intrusions (Attias, Bleich, & Gilat, 1996). These results reflect sensitivity and orientation to distracting traumatic information in PTSD.

However, the effect was not entirely specific to traumatic information, as the PTSD group failed to differentially respond to rare, neutral targets and the distracting combat pictures, whereas controls demonstrated larger P3 amplitude for neutral targets than distracter combat images (Attias, Bleich, Furman, & Zinger, 1996). Rather, PTSD subjects demonstrated enhanced P3 amplitude for both neutral targets and combat distracters. Nevertheless, there was some indication that the presence of traumatic images may have interfered with the capacity to respond to neutral, rare target images (domestic animals), as indicated by delayed P3 and reaction times in PTSD for the targets (Attias, Bleich, Furman, & Zinger, 1996). These initial ERP results partially support the proposition that activation of a trauma schema in PTSD can enhance traumatic, but interfere with neutral information processing, but only in relative terms, as the absolute magnitude of response for both increased in the presence of traumatic information (see Chemtob et al., 1988; Foa et al., 1989).

Several studies have further investigated the sensitivity of PTSD patients to emotional stimuli (Kounios et al., 1997; Stanford, Vasterling, Mathias, Constans & Houston, 2001; see also Shiffer, Teicher & Papanicolaou, 1995). Firstly, Kounios et al. (1997) report an ERP study of visual word stimuli that comprised common neutral or combat words and rare target food words. Their findings indicated smaller P100 over the right posterior temporal region, but enhanced P3 for both combat and neutral words; the study found no differential responses to combat and neutral words (Kounios et al., 1997). These findings confirm larger P3 amplitude for combat stimuli in PTSD and also similar findings of no differential P3 response between traumatic and neutral stimuli (e.g., Attias, Bleich, Furman & Zinger, 1996). As in the previous work, this

study indicates larger P3 for all stimuli in the presence of traumatic stimuli[1]. In contrast, Stanford et al. (2001) observed greater P3 activity for trauma words and smaller P3 activity for neutral words in PTSD patients, which is inconsistent with the earlier studies (Attias, Bleich, & Gilat, 1996; Attias, Bleich, Furman & Zinger, 1996; Kounios et al., 1997). They observed that an enhanced frontal P3 for trauma words was specific to trauma; it did not generalize to social threat words (Stanford et al., 2001). Thus, while these studies to date confirm an attention bias for trauma, they are inconclusive with respect to associated deficits in attention for neutral information (cf. Chemtob et al., 1988; Foa et al., 1989).

However, even this conclusion is compromised by one ERP study of emotional Stroop words, which indicated smaller and later P3 activity for all words in PTSD patients, even for trauma words (Metzger, Orr, Lasko, McNally & Pitman, 1997). For all combat veterans, this study confirmed delayed reaction times for traumatic words (which has been observed in emotional Stroop studies) and it demonstrated that trauma words are related to greater frontal P3 than neutral words (for both PTSD and control subjects). This larger P3 confirms that delayed response times for emotional Stroop words do reflect greater attention or evaluation for the emotive words. However, the PTSD subjects had smaller and later P3 ERPs than control subjects, so the PTSD patients were not allocating as much attention to those words as the control subjects. This finding is inconsistent with the previous literature and theory on attention bias in PTSD, which clearly predicts greater attention for trauma words in PTSD. A large proportion of research findings appear to support this hypothesis, so it is difficult to reconcile this study with both theory and previous work. Perhaps the differences between studies reflect variations in the degree of intrusive or avoidance symptoms in

[1] It is interesting to note that the frequency of presentation of combat stimuli was not a significant factor in the elicitation of enhanced responses; the previous work presented combat stimuli rarely, whereas this study presented them as common stimuli. Also, there appear to be no substantial differences between pictorial and word stimuli.

patients or the nature of control groups. The differences might also depend critically on the absolute or relative frequency of presentation for neutral, emotive, threat, or trauma stimuli. Further independent replication of this study would be valuable, with further consideration of intrusive and avoidance symptoms, control subjects, and frequency of stimulus presentations.

If the sensitivity to trauma is a solid finding, the question arises as to whether this sensitivity could be related to or extend to any emotional stimuli, not just traumatic stimuli. Blomhoff, Reinvang and Malt (1998) investigated the impact of auditory emotional words in PTSD. They argued that any emotional words might have a high propensity to be associated with trauma or traumatic emotions and thereby capture attention and elicit larger P3 activity. They used an auditory P3 oddball task with pure frequency common and rare target tones, while rare distracters were digitized spoken words, which comprised non-words, positive and negative emotion words (the non-words were garbled reversed sound waves of the positive and negative words, to maintain similar stimulus duration and "complexity"). They found no significant abnormalities to common and target tones in PTSD. It is very interesting to note that there was larger P3a for acoustic non-words in PTSD, suggesting an orientation of attention for the ambiguous distracter events, and this P3 amplitude for non-words was associated with arousal and intrusion symptoms. In contrast to these non-words, the emotive words elicit larger P3 activity, but there were no group differences in P3 amplitude for the emotion words (Blomhoff et al., 1998). The only indications of any relationship between PTSD and emotive word responses were associations of P3 amplitude with arousal and avoidance symptoms. In large part, this study failed to demonstrate a clear abnormality in processing emotion words in PTSD, so the findings suggest there is no clear generalization of the trauma sensitivity to any emotional information. Although this study employed a valuable task design, it failed to control

for important diagnostic criteria, including comorbid depression in PTSD patients and significant psychiatric disorders in the control group, including depression. Furthermore, it is not clear whether patients and controls were matched for important demographic and psychometric qualities, especially for premorbid intelligence. Hence, the results of the study must be considered tentative, pending replication with more rigorous methods. Thus, at this stage, the case for a general bias in information processing for PTSD patients is not very strong, given the failure of this study and similar work to clearly identify general abnormalities in PTSD responses to non-traumatic emotional information (see also Stanford et al., 2001; Kaufman, 2002).

However, there seems to be a good case for greater novelty sensitivity in PTSD. Blomhoff et al. (1998) presented highly ambiguous, novel distracters in the form of their non-word stimuli, which did elicit greater P3a and attention from PTSD patients. Moreover, this enhanced novelty response was related to intrusive symptoms (Blomhoff et al., 1998). Similarly, Kimble, Kaloupek, Kaufman and Deldin (2000) investigated an auditory three-tone task, with common (1000Hz), distracter (500Hz) and target tones (2000Hz), as well as an auditory novelty task, with the same common and target tones, but non-repeating novel sounds (clicks, buzzes, etc.). There were no differences in target reaction times or accuracy between combat veterans with or without PTSD. Also, there were no group differences in P3 amplitude for target or distracters within each task. These findings are inconsistent with prior findings from similar neutral auditory tasks (see discussion below of McFarlane, Weber & Clark, 1993; Charles et al., 1995; Boudarene & Timsit-Berthier, 1997; Metzger, Orr, Lasko & Pitman, 1997; Metzger, Orr, Lasko, Berry & Pitman, 1997). These differences might be explained by variations in patients or the control groups across studies (Kimble et al., 2000). However, there was an interaction of group by task for distracters, which comprised greater frontal P3 amplitude for novel than repeated distracters in PTSD (Kimble et al., 2000). The effect

identified persisted after adjustment for combat exposure and comorbid panic disorder (there was no correction for depression). Note that this finding required comparisons between the repeated distracters (a neutral pure tone) and the novel, ambiguous distracters (various clicks, buzzes etc.). With similar designs, it might be possible to explore the effects of emotional distracters. The novel sounds in this study were not associated with patient trauma and therefore suggest that PTSD patients are sensitive to not only trauma specific information, but also ambiguous novel stimuli. Furthermore, given a resource allocation model of attention and the greater novelty distraction of PTSD patients, it was expected they would have smaller P3 activity for targets. However, PTSD patients demonstrated similar deficits in target processing to the controls. That is, all subjects had smaller P3 activity for targets during the novelty task, indicating that novel distracters diverted attention from the primary task (Kimble et al., 2000). Unfortunately, Kimble et al. (2000) did not report any associations between novelty distraction and PTSD symptoms. Thus, several studies indicate greater novelty responses in PTSD patients.

1.3.3 Cognitive Neuroimaging

Insight into the neural networks engaged by traumatic information is provided by functional brain imaging studies of PTSD (Rauch et al., 1996; Shin et al., 1997, 1999; see also Rauch & Shin, 1997; van der Kolk, 1997; see also Villarreal & King, 2001). For example, Rauch et al. (1996) used positron emission tomography (PET) to investigate regional cerebral blood flow (rCBF) in PTSD patients during mental imagery of either traumatic or neutral experiences, prompted by listening to a prior tape recording of their own narration. For traumatic imagery, PTSD patients had increased rCBF in limbic and paralimbic structures of the right hemisphere, including medial orbitofrontal, anterior cingulate, insular, and anterior and medial temporal cortex, as well as the amygdala (Rauch et al., 1996; see also Rauch, Savage, Alpert, Fischman, &

Jenike, 1997). These regions appear to be engaged in the cognitive appraisal of emotional experience and the amygdala, in particular, is involved in detection of threat and generation of fear and associated autonomic and neuroendocrine responses (see LeDoux, 1990, 1995). The orbitofrontal and anterior cingulate regions may form part of larger executive attention network for orientation and emotional appraisal. A further increase in rCBF was identified in secondary visual cortex, possibly related to traumatic visualization. In contrast, decreases in rCBF were found in left inferior frontal cortex (Broca's area) and left middle temporal cortex, suggesting decreased linguistic cognitions during traumatic imagery, which may indicate that traumatic memories consist mainly of sensory and emotional elements, with less linguistic encoding or associations (Rauch et al., 1996; Shin et al. 1997; see also Fig, Liberzon, Steventon, Minoshima & Koeppe, 1995; Schiffer, Teicher & Papanicolaou, 1995; van der Kolk, 1997).

These initial findings were partially replicated by Shin et al. (1997), who investigated rCBF during (a) imagery of trauma, negative and neutral experiences and (b) visual presentations of trauma, negative and neutral stimuli (which were accompanied by an auditory description of the scene). This study did not identify increased activity in PTSD for combat pictures, compared with neutral pictures, which may be inconsistent with the ERP findings (e.g., Attias, Bleich & Gilat, 1996). Rather, there was decreased activity for PTSD patients in left middle frontal and anterior cingulate cortex. In contrast, the combat veterans without PTSD demonstrated increased activity for combat pictures in left middle frontal gyrus, Broca's area, left superior temporal gyrus and left supramarginal gyrus (which may indicate greater auditory-verbal processing for the emotive combat pictures). These findings are inconsistent with those to be expected, given relevant theory and prior findings from ERP studies; these findings suggest avoidance in the PTSD patients. The PET

procedure for blocked stimulus delivery is a continuous presentation of combat imagery, whereas rare combat images are given in ERP task paradigms, so a possible explanation for these findings of Shin et al. (1997) may be some degree of avoidance in the PTSD group, given a long, continuous presentation of combat images (a single-trial fMRI study may be more suitable). This is in contrast to the mental imagery condition, where voluntary activation of traumatic cognition is required. In fact, this study did identify increased ventral anterior cingulate activity in PTSD for combat imagery, compared with neutral imagery, which replicated the previous finding (Rauch et al., 1996). Furthermore, in a comparison between combat imagery with combat pictures, it identified increased activity in left middle frontal gyrus, left ventral anterior cingulate gyrus, left supramarginal gyrus and right amygdala. This suggests that previous findings of anterior cingulate and amygdala activity for traumatic imagery may be specific to the voluntary generation of traumatic cognitions.

Further work has confirmed enhanced responses in the amygdala for fearful expressions. Rauch et al. (2000) investigated functional magnetic resonance images (fMRI) from combat PTSD patients during a masked facial presentation, where facial expressions were either fearful or happy. These emotive faces were displayed very briefly (30 ms) and then masked by a longer neutral face expression (170 ms). This task design prevents controlled processing of the masked faces, thereby activating automatic emotional responses, with enhanced activity in the amygdala for the fearful faces. The results clearly demonstrated greater activation of the left amygdala for fearful faces, with PTSD patients demonstrating larger activity than combat veterans without PTSD (Rauch et al., 2000).

In a similar study of responses to emotive faces, Felmingham, Bryant and Gordon (2003) employed ERPs at occipital and posterior temporal scalp sites to measure early cortical responses to emotive faces (angry and neutral faces). They did not use a

masked presentation design; instead they presented alternating angry and neutral faces, with only passive viewing required. They reasoned that automatic emotive responses could induce a feedback modulation of visual cortical processing in striate and extrastriate face perception regions. Prior reports had identified enhanced responses to emotive stimuli between 80-160 ms over fronto-central and posterior scalp regions. Similarly, they identified an enhanced negative peak at 110 ms over occipital and posterior temporal sites for angry vs. neutral faces in non-psychiatric control subjects (Felmingham et al., 2003). These ERP components for PTSD patients were smaller and slower than normal; they also failed to discriminate between the angry and neutral facial expressions (Felmingham et al., 2003). Felmingham et al. (2003) interpret these findings as a refutation of the generalized threat sensitivity hypothesis in PTSD. Rather, they propose the findings are explained by a general failure of sensory discrimination processes. While this may be true, another possibility is that sensory processing of all stimuli in this study were inhibited by top-down avoidance processes, given that stimuli were regular, predictable and they were not masked. This could be consistent with both generally smaller amplitude and later peak activity of even the early visual ERP components. As in the study of Shin et al. (1997), passive viewing of threat or trauma images may not reveal enhanced responses in PTSD patients, who are likely to engage avoidance processing strategies. Rather, the enhanced sensitivity to threat and trauma stimuli appears to be a transient effect for masked and rare novel stimuli, which may escape top-down avoidance processing and engage novelty attention processes. The only other paradigm to elicit these responses is script-driven imagery, which requires voluntary sustained attention for traumatic emotions and cognitions.

1.3.4 Peripheral Physiology

The activation of a trauma network is associated with a peripheral fear or stress response and the feedback from that response reinforces the impact of the initial

cognitive and affective appraisal. Psychophysiology studies demonstrate that traumatic cues or mental imagery in PTSD provokes heightened startle responses and peripheral physiological hyperactivity, including increases in heart rate and blood pressure, muscle tension, and skin conductivity (Blanchard, Kolb, Pallmeyer, & Gerardi, 1982; Brende, 1982; Blanchard, Kolb, Gerardi, Ryan, & Pallmeyer, 1986; Pallmeyer, Blanchard, & Kolb, 1986; Pitman, Orr, Forgue, de Jong, & Claiborn, 1987; Gerardi, Blanchard & Kolb, 1989; Pitman et al., 1990; Blanchard, Kolb, & Prins, 1991; Orr, Pitman, Lasko & Herz, 1993; Orr, 1994). Murburg (1997) points out interesting peripheral relationships to central processes. For instance, traumatic visualizations may induce increased peripheral epinephrine concentrations that increase memory consolidation by stimulating the amygdala, which is important in emotional stimulus evaluation and memory (see also LeDoux, 2002; McGaugh, 2002). Murburg (1997) notes that, "responding to a stressor … may itself leave behind molecular 'memory traces' that so alter involved neural pathways as to predispose them to be more readily activated in the future". Reduction of such physiological responses to traumatic imagery during psychotherapy promotes recovery from PTSD, which also suggests the importance of visceral reinforcement for the initiation and maintenance of a trauma schema (Boudewyns & Hyer, 1990; cf. Pitman et al., 2002; Vaiva et al., 2003).

1.3.5 Summary

These research studies have demonstrated a heightened sensitivity to trauma information in PTSD, which is apparent in both cognitive and peripheral responses. Cognitive studies have shown that this sensitivity is apparent in attention and memory tasks and that it is positively associated with the severity of intrusive symptoms. ERP work has shown enhanced responses for trauma stimuli in both early sensory (N1) and later stimulus evaluation (P3) processes; PTSD patients fail to discriminate relevant from irrelevant stimuli, they process irrelevant trauma stimuli to the same degree as

significant target events. The ERP studies do not clearly demonstrate that trauma sensitivity extends to the processing of any emotional information, rather the sensitivity appears to be specific to trauma. An important aspect of research design is the manipulation of stimulus novelty, with several ERP studies indicating heightened novelty responses in PTSD, even for non-traumatic stimuli. Furthermore, failure of some studies to elicit enhanced responses to trauma stimuli may be due to extended presentation of traumatic information, which elicits avoidance strategies in PTSD patients. The sensitivity to trauma information may be dependent on brief and possibly rare trauma stimulus presentations.

Neuroimaging demonstrates that voluntary trauma imagery is associated with increased activity in limbic and paralimbic structures (including medial orbitofrontal, anterior cingulate, insular, and anterior and medial temporal cortex, as well as the amygdala). These areas are engaged in emotional evaluation, learning and memory. An important contribution to the maintenance of trauma sensitivity could be feedback into these areas from peripheral stress responses.

1.4 Research Evidence: Neutral Information Processing

In contrast with studies of trauma sensitivity and intrusions, studies of neutral information processing often report deficient responses in PTSD. Abnormal hippocampal functions may contribute to difficulties with perceptual discrimination and integration of new information into episodic memory (Kolb, 1987; Everly, 1989, 1993; see also Gray, 1982a).

1.4.1 Neuropsychology

Neuropsychological investigation of PTSD shows deficits of attention and executive functions (Gil, Calev, Greenberg, Kugelmass, & Lerer, 1990; Uddo, Vasterling, Brailey, & Sutker, 1993; see also Lezak, 1995). These deficits are observed

in the performance of various tasks, including a continuous performance task, verbal fluency, comprehension, similarity judgments, digit-symbol substitution, and automatic tasks such as counting backwards, counting forwards by threes, and reciting the alphabet. Several neuropsychology studies also demonstrate memory impairments in PTSD; including immediate memory impairments in both verbal and visual tasks (Everly and Horton, 1989; Gil et al., 1990; Bremner et al., 1993; Uddo et al., 1993) and some studies identify long-term memory deficits for verbal tasks and famous events (Gil et al., 1990; Bremner et al., 1993), but results for visual tasks are equivocal (Bremner et al., 1993; Uddo et al., 1993). Also, several studies have identified deficits of auditory verbal learning and memory (Uddo et al., 1993; Yehuda et al., 1995). Thus, neuropsychology studies employ trauma-neutral tasks to clearly demonstrate impairment of diverse executive cognitions in PTSD.

1.4.2 Cognitive Psychophysiology

Cognitive psychophysiology enhances our understanding of the brain systems impaired during neutral information processing in PTSD. Recent neuroimaging studies provide insights into the sensory discrimination, attention and working memory processes of PTSD.

Paige et al. (1990) employed ERPs to investigate responses to increasing auditory intensity in PTSD. Veterans with PTSD show normal increases in N100, but abnormal decreases in P200 amplitude as auditory intensity increases toward and above the startle threshold (the effect was more prominent in the left than the right temporal area). Paige et al. (1990) propose that the decrease of P200 amplitude reflects a process of "protective inhibition" in response to intense stimuli - PTSD patients inhibit stimulation that would otherwise overload their capacity for accurate discrimination. Lewine et al. (1997) replicated this study with combined EEG and magneto-encephalography (MEG), which indicated that the P200 reduction effects are located in the auditory association

cortex and that the effect is a decrease in cortical activity (i.e., dipole moment) rather than variation in the location of cortical source activity. These results suggest a cortical, rather than subcortical, abnormality.

However, studies have investigated earlier subcortical habituation effects, indicated by the auditory P50 ERP (Gillette et al., 1997; Neylan et al., 1999; see also Shalev et al., 1988). These studies have shown that PTSD patients do not habituate the P50 response for non-startle repeated clicks, suggesting an abnormality of sensory gating in brainstem and thalamic circuits.

This evidence can be interpreted in the context of hypotheses about abnormal interactions among subcortical, limbic and cortical networks (e.g., Gray, 1982a; Kolb, 1987; Everly, 1989, 1993). In particular, the evidence supports the proposal that trauma leads to hyperarousal or hypersensitivity of sensory systems. If brainstem and thalamic circuits fail to habituate to neutral stimuli, their cortical projections are overloaded by irrelevant, repetitive information, leading to abnormal sensory processing. Thus, these studies provide some evidence to support an abnormality of sensory discrimination processes predicted by Kolb (1987). The evidence supports an inference that patients have a lower threshold at which sensory discrimination is overloaded by intense stimulation, promoting earlier inhibition of excessive stimulation. The primary auditory cortex demonstrates a stimulus driven response, with N100 augmentation to increasing stimulus intensity, but the auditory association cortex demonstrates active inhibition of excessive stimulation (i.e., P200 reductions). It may be that only at the level of associative cortical control can the nervous system counteract what is otherwise an imbalance in relatively automatic systems. Kolb (1987) hypothesized that frontal cortical systems for executive control of subcortical brainstem and other thalamic circuits may be deficient. The efficient modulation of elementary sensory discrimination processes is important for adaptive stimulus information processing, so

this initial confirmation of Kolb's (1987) proposal of impaired sensory activity in PTSD forms an important contribution to understanding PTSD.

These early sensory abnormalities are accompanied by later cognitive disorders. In an ERP study of auditory discrimination, McFarlane et al. (1993) employed a three-tone discrimination task (similar to a conventional oddball task, but with rare distracter and target tones), where all stimuli presented had a constant duration and sub-startle intensity. Even for these neutral tones, PTSD patients had a slower response time and both later N2 and smaller P3 ERPs for infrequent target tones and no clear differentiation of P3 amplitude for target and distracter tones (see replications by Charles et al., 1995; Boudarene & Timsit-Berthier, 1997, who also demonstrate diminished frontal CNV in PTSD; cf. Knott & Irwin, 1973; Shalev et al., 1988). These findings implicate cortical processing engaged in sensory discrimination, stimulus evaluation and working memory processes. The N2 ERP indicates difficulty with initial discrimination of auditory features (see Näätänen, 1992), while the later diminution of P3 reflects a difficulty in the conscious evaluation of the significance or relevance of a stimulus (see Duncan-Johnson & Donchin, 1977; Johnson, 1988). In a further study of the latter effect, subjects were required to detect consecutive repeats in a five tone discrimination task, which required frequent updating of the physical attributes of target tones (Galletly, Clark, McFarlane & Weber, 2001). Smaller P3 activity for common and target tones indicated deficits in working memory processing for PTSD patients (Galletly et al., 2001). Thus, these studies extend the findings of abnormal thalamic and early sensory processing to later aspects of cortical processing engaged in stimulus discrimination, evaluation and working memory integration.

The P3 abnormality in PTSD may reflect catecholamine dysfunction. Kolb (1987) hypothesized that sensory discrimination is affected by catecholamine neurotransmission, either directly or indirectly, providing an important theoretical link

between neurophysiology and cognition (see also Gray, 1982a; McFarlane et al., 2002). There is evidence that catecholamine neurotransmission, especially noradrenaline, contributes to attention modulation of cortical stimulus processing (e.g., Clark, Geffen & Geffen, 1987). Moreover, noradrenaline increases the amplitude of P3 ERPs (see discussion in McFarlane et al., 1993; Boudarene & Timsit-Berthier, 1997). Further indications of the role of catecholamines was found in a study of combat-related PTSD and women who were sexually abused as children, which demonstrated similar deficits in P3 for target events, but also showed that medicated patients had normalized P3 amplitudes (Metzger, Orr, Lasko & Pitman, 1997; Metzger, Orr, Lasko, Berry & Pitman, 1997). These findings suggest a role for pharmacological treatment of the P3 deficit and they may provide support for Kolb's (1987) hypothesis of abnormal catecholamine influences on cognitive processes in PTSD.

These findings of abnormal P3 in PTSD can be modified by symptom severity and comorbidity. There are decreases in P3 and slower reaction times with dissociative and numbing symptoms (Kaufman, 2002; Felmingham, Bryant, Kendall & Gordon, 2002), as well as depression symptoms (Metzger, Orr, Lasko & Pitman, 1997; cf. Kaufman, 2002). There are increases in P3 with panic symptoms (Metzger, Orr, Lasko & Pitman, 1997; Metzger, Orr, Lasko, Berry & Pitman, 1997; see also Clark, McFarlane, Weber & Battersby, 1996). Furthermore, the abnormality in P3 processes is not specific to PTSD, it has been observed in diverse psychiatric conditions, which suggests a central role for these processes in integrated cognition.

The nature of neutral stimulus processing in PTSD should vary with affective states. That is, attention bias theory would predict that under conditions of stress or traumatic affective induction, the attention available for neutral stimuli might be impaired. However, Kaufman (2002) found no effects of affective state on P3 for neutral stimuli. Unlike previous work that has either included threat or trauma content

into task materials or ensured that all task materials and the emotional context are neutral, this study employed a neutral three-tone auditory discrimination task with prior induction of an affective context. Across three affective contexts, neutral, stressful and traumatic, there were no modulations of the P3 effects for neutral stimulus processing in the three-tone auditory discrimination task (Kaufman, 2002). However, the emotional context did have an impact on dissociative states, which were related to P3 effects for distracters (Kaufman, 2002; cf. Blomhoff et al., 1998). This study suggests that attention biases are not simply a result of general affective states, but rather they arise as specific responses to particular information and they could be especially dependent on the novelty or distraction properties of the information.

1.4.3 Cognitive Neuroimaging

Some preliminary neuroimaging evidence demonstrates abnormal activity in parietal attention systems during neutral stimulus processing in PTSD. Semple et al. (1993, 1996) found evidence of a deficit in attention for neutral information in PTSD (although their patient group had a comorbid substance abuse). They investigated rCBF in veterans with PTSD during an auditory continuous performance task (CPT), which required vigilant attention and discrimination for rare target events. PTSD patients had poor discrimination of targets and a diminished rCBF in the angular gyrus of the right parietal cortex, a brain region that is implicated in multimodal attention processes (Semple et al., 1993, 1996; see also Posner & Raichle, 1994). The rCBF in the parietal cortex was positively associated with the accuracy of performance (Semple et al., 1993, 1996). The authors suggest that their results are due to PTSD more so than substance abuse, because the patients abstained from substance use for several weeks before the study and the findings were not consistent with similar findings in a patient group with substance abuse alone (Semple et al., 1993, 1996).

In several papers associated with the present thesis, we have demonstrated abnormal functional brain activity in PTSD for neutral stimuli (Shaw et al., 2002; Clark et al., 2003; see also Clark et al., 2000). PET was recorded during the presentation of several neutral, visuo-verbal tasks, using the same stimuli, but different task instructions. In one version, the identity of a target word remains fixed, while the other version requires detection of any repeated words (providing a variable target identity). The latter task demands greater verbal working memory updating. In controls, activation was identified in several nodes of a distributed cortical network, including the dorsolateral prefrontal cortex, the orbitofrontal cortex and anterior cingulate, as well as the supramarginal gyrus of the inferior parietal lobe (Clark et al., 2000; Shaw et al., 2002; Clark et al., 2003). However, PTSD patients demonstrated a deficit in prefrontal activity, especially in the left dorsolateral prefrontal cortex, with possible compensation apparent in greater activity in the parietal nodes of the network (Shaw et al., 2002; Clark et al., 2003). This pattern of activity is taken to indicate deficits in prefrontal processes engaged in controlled manipulation of working memory content, which may be stored as multimodal representations in posterior parietal regions. The greater activity in the latter regions, especially the posterior aspects of the superior parietal lobe, may indicate more reliance on visuo-spatial information encoding and manipulation than more abstract symbolic representations, which would involve prefrontal nodes (Clark et al., 2003). The deficit in left prefrontal activity may be associated with decreased verbal skills in PTSD, which has been observed in studies of traumatic information processing (e.g., Rauch et al., 1996). In contrast with those studies of trauma imagery, activation was identified in the middle frontal gyrus, which is implicated in not simply speech production (which is associated with inferior frontal gyrus, Broca's area), but more complex linguistic or procedural manipulation and integration of information in working memory (this is further discussed, at length, in following chapters). Thus, this

work demonstrates a more fundamental difficulty with manipulating neutral linguistic information in working memory in PTSD, which is consistent with theories about the dissociation of traumatic memory from linguistic, narrative encoding (e.g., van der Kolk, 1997).

1.4.4 Summary

Studies of neutral information processing, in the absence of trauma stimuli, comprise neuropsychology, psychophysiology and neuroimaging reports. The neuropsychology studies indicate deficits in various attention and memory tasks, including verbal and visual processes. Several ERP studies demonstrate abnormal thalamic gating and early sensory processing for auditory tones in PTSD. Furthermore, there is also evidence for abnormal stimulus discrimination, evaluation and working memory integration, indicated by abnormal N2 and P3 ERPs in PTSD. These cognitive deficits may be related to abnormal catecholamine neurotransmission. Several studies of rCBF have demonstrated abnormal activity in frontal and parietal systems engaged in executive functions (attention and working memory).

1.5 CONCLUSIONS

A traumatic experience can promote development of a sensitive, coherent, and stable trauma schema, often consisting of sensory, affective, and intentional information that may be dissociated from linguistic, symbolic representation. This trauma schema predisposes PTSD patients to attend to and remember traumatic information and associated trauma cues. Cognitive and electrophysiological studies have demonstrated heightened sensitivity for traumatic and possibly novel stimuli in PTSD. Of particular interest are the ERP studies that show early, automatic allocation of attention to identification and discrimination of traumatic stimulus attributes and greater conscious attention to the significance or meaning of traumatic images. Also, neuroimaging

indicates greater activation in the limbic system during traumatic recollection, especially the amygdala, with associated abnormalities in orbitofrontal and anterior cingulate regions. This work also demonstrates that traumatic recollection is associated with diminished activity in left inferior frontal cortex, which suggests that traumatic memories consist of sensory and emotional elements without concomitant linguistic associations. It is important to note that many of these studies demonstrate an association between trauma sensitivity and the severity of PTSD symptoms, especially traumatic intrusions, and that the trauma sensitivity may remain after recovery from PTSD. Also, there are peripheral concomitants of a cognitive sensitivity to trauma, including abnormal neuroendocrine and autonomic arousal, which can reinforce cognitive and affective appraisals. Moreover, desensitization of those peripheral physiological responses to traumatic imagery can play an important role in recovery from PTSD.

A bias toward traumatic cognitions may interrupt the appropriate development of adaptive information processing structures related to neutral circumstances. There is no conclusive evidence of deficits in neutral information processing in the concurrent presence of trauma information. However, there is considerable evidence of abnormal neutral information processing in PTSD, in the absence of traumatic information. There is support for the neuropsychological theory of Kolb (1987) in the ERP research that demonstrates greater protective inhibition in PTSD sufferers (suggesting the threshold at which accurate discrimination occurs is lower in PTSD patients, promoting earlier inhibition of excessive stimulation; Paige et al., 1990). Further ERP research has also demonstrated a difficulty in the conscious evaluation of the significance or relevance of stimulus information (McFarlane et al., 1993; Charles et al., 1995; Metzger et al., 1997; Galletly et al., 2001). This latter difficulty has also been related to abnormal rCBF in several nodes of a cortical network engaged in attention and working memory processes

(Semple et al., 1993, 1996; Clark et al., 2003). There is also evidence of susceptibility to novel distraction in PTSD (e.g., McFarlane et al., 1993; Blomhoff et al., 1998; Kimble et al., 2000), which could be related to abnormal hippocampal, parahippocampal and prefrontal attention systems engaged in contextual novelty processing.

1.6 Overview of The Following Chapters

Recent research of attention and memory in PTSD is evolving within this context and that of recent developments in cognitive neuroscience. The latter research provides important insights into the neuroanatomy and neurophysiology of executive processes, including attention and memory. The challenge before the present work is to dissect and assess components of attention and memory for neutral information in PTSD, using the fine temporal resolution of ERPs, and to interpret these components in terms of constructs from both cognitive psychology and the emerging models of cognitive neuroscience. The focus here is on neutral information processing, as the integrity of this cognition may be a determinant of the onset and maintenance of PTSD. It can be seen from the context above, that we are not very clear about the relative contributions of early sensory attention and later working memory processes to the deficits in neutral information processing observed in PTSD. In terms of neuropsychology, we are not very clear about the relative contributions of subcortical and primary cortical activity engaged in early sensory filtering versus secondary and associative cortical systems engaged in working memory processes. The purpose of this thesis is to explore the role of these processes in a specific cognitive paradigm that compares the contributions from attention and working memory to neutral information processing. The following short chapter describes these aims and the design of this study. Then, a general method chapter follows, which covers all studies in this thesis, as the design of this work

required a single, comprehensive method for data acquisition and analysis. Following the method are three chapters that assess specific elements of cognitive systems in PTSD: (a) attention, (b) working memory updating, and (c) target detection. These chapters review relevant cognitive neuroscience, especially ERP studies, to facilitate operational definitions of cognitive constructs such as attention and working memory.