The Effects of Early Adversity on Adult Spatial Cognition: a Functional Magnetic Resonance Imaging Study.

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COMPULSORY DECLARATION

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

Signature:_____ Date:_____

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ABSTRACT

Exposure to traumatic childhood events can lead to a range of behavioural, psychological, and physiological consequences. Previous studies have shown that neurobiological changes in reaction to severe stress may cause lasting damage to particular neural regions, including the hippocampus and the prefrontal cortex. It has been suggested that such damage to these regions results in difficulties in associated cognitive functioning, including problems with verbal declarative memory and cognitive control. Little focus has been placed on visual-spatial cognition in traumatised individuals, however. The aim of this project, which comprised two studies, was to investigate visual memory and spatial cognition in adult survivors of childhood trauma. Study 1 compared the performance of 23 individuals who had experienced childhood abuse (the Trauma group) to 38 matched controls with no such experience (the Control group) on the four visual-spatial memory tasks of the Cambridge Neuropsychological Test Automated Battery (CANTAB). Results suggested that participants in the Trauma group showed poorer performance on two of the more complex tasks, which tapped both hippocampal and prefrontal cortex functioning, compared to the controls. One interpretation of this finding is that these between-group differences reflect the dysfunction of a network involved in visual-spatial memory in individuals who have experienced childhood trauma. Study 2 used functional magnetic resonance imaging (fMRI) to investigate whether any marked differences in neural activation would be evident between individuals with a history of childhood trauma (n = 7) and matched controls with no such history (n = 14) during spatial navigation tasks. Functional images were gathered while participants completed two spatial navigation tasks: the Computer-Generated Arena (CG Arena), a small-scale spatial navigation task, and the Virtual City, a large-scale spatial navigation task based on an environment created by Maguire et al. (1998). Although no significant behavioural differences were evident during the completion of these tasks, the fMRI data did show marked differences in activation. These results of the CG Arena, in particular, showed lower activation in PFC areas, including the anterior cingulate cortex, during wayfinding tasks. Taken together, the results of these two studies suggest that (a) subtly impaired neural functioning is evident in individuals with a history of childhood trauma, and (b) this impairment may lead to difficulties in successfully completing complex visual-spatial memory and spatial navigation tasks.

GENERAL INTRODUCTION

Exposure to early adverse events, such as childhood sexual and physical abuse, is associated with a range of behavioural, psychological, and physiological consequences. Physiologically, high levels of stress lead to hormonal and cardiovascular reactions that can affect a person's body (particularly the kidneys, pancreas, and heart) directly (Caffo, Forresi, & Lievers, 2005; McEwen & Sapolsky, 1995; Sapolsky, 2004). Stress can also disrupt eating and sleeping habits, digestion, and reproduction (Kemeny, 2003).

Childhood trauma is also associated with psychopathology and behavioural problems (Wonderlich et al., 2007). Adult psychopathological correlates of childhood trauma include symptoms of posttraumatic stress disorder (PTSD) and other anxiety disorders, as well as symptoms of depression and personality disorders (Caffo et al., 2005; Janssen et al., 2004; Maaranen et al., 2004; Meiser-Stedman et al., 2007; Sebre et al., 2004; Stallard, Salter, & Velleman, 2004). Furthermore, exposure to trauma during childhood is associated with a range of cognitive impairments, particularly involving memory (Bremner et al., 1995; Bremner, Vermetten, Afzal, & Vythilingam, 2004; Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2002; Shin, Rauch, & Pitman, 2006; Vasterling & Brewin, 2005). This study aims to explore the impact of childhood trauma on adult cognitive functioning, particularly in the domain of spatial cognition.

Trauma Exposure in South Africa

There is much research to show that, in South Africa, the risk of an individual being exposed to traumatic events[1] is relatively high compared to that in developed countries. For instance, a study investigating the prevalence of trauma exposure in a South African township found that out of the 201 participants, 94% reported having been exposed to at least one traumatic event (Carey, Stein, Zungu-Dirwayi, & Seedat, 2003). These data are congruent with those from cross-sectional studies of youth in rural and urban communities,

[1] The fourth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychological Association, 1994, pp. 467-468) states that in order for an event to be considered 'traumatic' both of the following have to be present: (a) The person experienced, witnessed or was confronted with an event that involved actual or threatened death or serious injury or a threat to the physical integrity of self or others, and (b) the individual's response involved fear, helplessness or horror. This definition, while encompassing many events, may prove insufficient in certain cases (Yule, 1999) and thus for the purposes of this study is defined thus: any event in which the person was exposed to an external stimulus that is perceived as threatening or harmful, and that causes the individual significant distress.

who reported exposure to violence ranging from 67% to 95% (Ensink, Robertson, Zissis, & Leger, 1997; Peltzer, 1999). Similarly, Ward and colleagues (2001) found that, in a sample of 104 Cape Town adolescents, 71% had either witnessed or been a victim of violence in which they knew the perpetrator, and 83% had been a victim of or witnessed violence in which a stranger was involved. Furthermore, Seedat, Nyamai, Njenga, Vythilingam, and Stein (2004), in their survey of 1140 boys and girls (mean age: 15.9 years) in Cape Town schools, found that 83% had been exposed to at least one traumatic event. Fifty-eight percent of the sample had witnessed violence in their community, 34% had been robbed or mugged, 33% had seen family members injured, beaten, hurt, or killed, and 14% had been victims of sexual assault.

This high rate of exposure to violence and abuse in South Africa is especially poignant when considering the physiological, psychological, and behavioural dysfunctions that are associated with traumatic experiences.

Trauma-Related Symptomatology

Across a wide range of age groups and population types, trauma exposure during childhood and adolescence is associated with a high risk of developing a range of different behavioural and psychological problems in adulthood. The most common psychopathological consequences of early childhood trauma are self-injurious behaviour (SIB), PTSD and other anxiety disorders, depression and other mood disorders, personality disorders, disorders related to substance abuse, sexual behaviour problems, positive psychotic symptoms, and somatoform and psychological dissociation (Caffo et al., 2005; Janssen et al., 2004; Maaranen et al., 2004; Meiser-Stedman et al., 2007; Sebre et al., 2004; Stallard et al., 2004; Wonderlich et al., 2007). Physical symptoms commonly resulting from early childhood trauma include chronic pain and gastrointestinal problems (Hodge et al., 2007; Krystal, 1978; Spertus, Yehuda, Wong, Halligan, & Seremetis, 2003; Teicher, Glod, Surrey, & Swett, 1993).

Exposure to severe stress and trauma early in life also leads to certain neurobiological events that can cause significant and lasting changes in brain development. Neuroscientists and neuropsychologists are able to describe, with some accuracy, the impact of psychological trauma on particular parts of the brain, and can therefore make predictions about the kinds of cognitive impairment that might follow in adulthood.

In moments of stress, activation in numerous brain regions and neurotransmitter systems allows an individual to assess the situation and to respond appropriately. It would appear that this process serves a protective role and facilitates appropriate reactions to

stressful situations (Sapolsky, Romero & Munck, 2000). However, a large body of research has suggested that, for certain people, neurobiological responses to fear and stress may prove maladaptive and may contribute to the development of psychopathology (PTSD, in most cases; Southwick, Yehuda, & Morgan, 1995; Vasterling & Brewin, 2005).

Researchers have identified a number of brain regions that are impacted by traumatic experiences; these include the prefrontal cortex (PFC), the amygdala, the hippocampus, the dorsal raphe nucleus, and the locus coeruleus. Three neurotransmitter systems have also been identified as playing an important role in stressful situations: (a) the noradrenergic system, (b) the serotonergic system, and the (c) hypothalamic-pituitary-adrenal (HPA) axis (Vasterling & Brewin, 2005).

The noradrenergic system is primarily associated with the locus coeruleus, which contains the majority of noradrenergic cell bodies in the brain. Functionally, this system seems to play a role in orientation to novel stimuli, alertness, vigilance, selective attention, and cardiovascular responses to life-threatening stimuli (Aston-Jones, Raikowski, Kubiak, & Alexinsky, 1994). If stimulated by an external stressor, it elicits fear responses and increases the release of norepinephrine in the amygdala, hippocampus, hypothalamus and the PFC (Zigmond, Finlay, & Sved, 1995). Exposure to severe stress and the subsequent flooding of norepinephrine in these regions can result in impaired functioning in these regions. For example, the increase of norepinephrine in prefrontal areas may lead to difficulties in executive functioning (e.g., problems with inhibition, attentional control and working memory; Arnsten, 2000; Birnbaum, Gobeske, Auerbach, Taylor, & Arnsten, 1999).

The serotonergic system is primarily associated with the raphe nuclei of the brainstem, which contain almost all the neurons involved in releasing serotonin (Nestler, Hyman, & Malenka, 2001). These neurons project to multiple brain regions, including the PFC and the hippocampus, and are involved in the regulation of these regions. Stressful situations cause an increase in the release of serotonin, which lead to dysfunctions in the hippocampus, amygdala and the orbitofrontal cortex, which is located in the PFC (Bremner et al., 2003; Koenen et al., 2001).

The release of glucocorticoids (corticosterone in rats, cortisol in humans) is regulated by the action of the HPA axis (Anderson et al., 2007). The HPA axis is a closed-loop neurocircuit controlled by a regulatory set of afferents, consisting mostly of the neurons in the paraventricular region of the hypothalamus. As the brain acknowledges the presence of a stress-eliciting stimulus, these neurons secrete corticotrophin-releasing hormones (CRF), which stimulates the anterior pituitary gland to release adrenocorticotrophic hormones

(ACTH), which in turn leads to glucocorticoid secretion from the adrenal gland. Glucocorticoid secretion then regulates the entire HPA axis by providing negative feedback to terminate subsequent CRF and ACTH release (Bowman, 2005). An increase in glucocorticoids has been shown to disrupt functionality in both the PFC (Roozendaal, McReynolds, & McGaugh, 2004) and, particularly, in the hippocampus (Het, Ramlow, & Wolf, 2005; Kim & Diamond, 2002; McEwen, 2000; Newcomer et al., 1999).

In summary, external stressors cause certain brain regions to release stress hormones, which in turn affect neural networks and thus influence behaviour and cognition. This systemic impact suggests that multiple networks are involved in human reactions to a traumatic stimulus.

As mentioned above, the PFC is heavily affected by the release of stress hormones. Within the PFC, the anterior cingulate cortex (ACC) has been a particular region of interest for researchers studying the effects of trauma exposure. Studies have shown a diminished response in ACC activation during the presence of emotional stimuli in patients with PTSD. It is speculated that this diminished activity may mediate symptoms of distress and arousal when individuals with PTSD are exposed to reminders of the trauma (Bremner et al., 1999; Shin et al., 2005, 2007; Williams et al., 2006). One recent study investigated the neural functioning of arousal networks in 11 patients diagnosed with PTSD and 11 age- and sex-matched non-traumatised controls. The authors hypothesized that the ventral ACC is involved in regulating arousal networks, and that reduced activity, in the PTSD group, in this region would be evident during an oddball task that required the participants to respond to salient, non-trauma-related auditory target tones embedded in lower frequency background tones. Participants were instructed to make button-presses when they heard the target tones and skin conductance response (SCR) was used to indicate when arousal networks were engaged. Results confirmed that there was a reduction in ventral ACC activation in the PTSD group during these tasks, specifically when arousal networks were engaged (Felmingham et al., 2009).

These data are consistent with those from studies that have shown bilateral reductions in ACC volume in individuals with a history of trauma exposure. Kitayama, Quinn, and Bremner (2006) performed magnetic resonance imaging (MRI) on eight adults with PTSD and 13 healthy matched controls. The individuals diagnosed with PTSD showed statistically significantly reductions in right ACC volume, with non-significant reductions in left ACC volume. Similarly, Woodward (2004) analysed ACC volumes in 38 war veterans with combat-related PTSD and 25 traumatised non-PTSD veterans. His findings also suggested

that PTSD is associated with reduced ACC volume, and that this reduction is consistent with cingulate hypofunctionality involved in the disorder.

This ACC hypofunctionality is most often reflected by impairments in working memory and selective attention (MacDonald, Cohen, Stenger, & Carter, 2000). Many studies of the ACC have involved its executive functioning in conflict monitoring and in making adjustments in attentional control (Braver, Paxton, Locke, & Barch, 2009; Veen et al., 2001). For example, Kerns et al. (2004) used the Stroop colour-naming task to assess ACC functioning in 23 healthy participants who completed a conflict-monitoring task. Conflict resolution in the task (i.e., naming the colour of the ink in which a word is printed, rather than reading the word itself; e.g., saying "green" when the word "red" is printed in green ink) requires behavioural adjustments and cognitive control. A direct relationship was evidenced between ACC activity on high conflict trials and behavioural adjustments. Increased ACC activity was found on trials that preceded behavioural adjustment. This suggests that the ACC recognises the conflict in the task and engages cognitive control that prompts the individual to make the appropriate changes in their behaviour. These adjustments were also associated to increases in PFC activity during high conflict trials. The results confirmed the hypothesis that ACC involves a conflict-monitoring function and that the engagement of this function is responsible for the recruitment of cognitive control.

The role of the ACC in executive functioning, and the association of ACC hypofunctionality with traumatic exposure, suggest that dysfunctions in attentional control may be evident in individuals who have experienced a traumatic event.

Another brain region of particular interest for researchers interested in the cognitive implications of traumatic stress is the hippocampus. The fact that this structure and its neural connections are involved in both learning and new memory formation, and that it has been identified as a region affected by stress, makes it of particular importance for the purpose of this study.

The Hippocampus

The hippocampus is critically involved in learning and the formation of new memories (Squire, Cohen, & Nadel, 1984; Squire, Knowlton, & Musen, 1993). Furthermore, numerous studies have shown that, via hippocampal mechanisms, exposure to high levels of stress and trauma can affect memory in both animals (e.g., Diamond, Park, Heman, & Rose, 1999; Sandi et al., 2005; Sapolsky, Krey, McEwen, 1986; Topic et al., 2007; Xiang, Hao, & Deng, 2006) and humans (e.g., Bremner, 2001; Carrion, Weems, & Reiss; 2007; Lupien et

al., 1994; Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Newcomer et al., 1999; McLaughlin, Gomez, Baran, & Conrad 2007).

Neuroanatomically, the hippocampus forms part of the hippocampal formation, which is located deep within the medial temporal lobe. The gross anatomical image of the hippocampal formation is a distinct bulge in the floor of the temporal horn of the lateral ventricle, which is widest at its rostral extent where it bends towards the medial surface of the brain. The main body of the hippocampal formation gets progressively thinner as it bends dorsally toward the splenium of the corpus callosum. This latter structure is connected to various brain regions including the basal forebrain, the entorhinal cortex, hypothalamic and thalamic structures, the neocortex, and the amygdaloid complex. The hippocampus also receives inputs from the brain stem and, furthermore, has numerous intrinsic connections (Anderson et al., 2007).

Structurally and functionally, the hippocampus proper can be divided into two hemispheres: the right hippocampus, which is primarily associated with visual-spatial memory (Smith & Milner, 1981) and the left hippocampus, which is primarily involved in verbal declarative memory (Frisk & Milner, 1990).

More specifically with regard to functionality, the hippocampus is part of a system critically involved in the encoding and retrieval of long-term declarative memories. Functional magnetic resonance imaging (fMRI) studies have correlated observed hippocampal activity with encoding success (Davachi et al., 2003; Paller & Wagner, 2002; Kirwan & Stark, 2004; Reber et al., 2002; Stark & Okado, 2003; Strange et al., 2001). For instance, Davachi and Wagner (2002) investigated neural activity in 16 healthy participants during the performance of two verbal encoding conditions. Under one condition, participants were required to perform item-based maintenance of word triplets in working memory. Under the second, they were required to form inter-item associations among the words in each triplet. Results indicated that the hippocampus was engaged during both tasks, but relational processing (in the second condition) elicited a greater hippocampal response. This study, therefore confirmed the hippocampus' involvement in the encoding of new information.[2]

Similarly, many fMRI studies have illustrated the role of the hippocampus in memory retrieval. This research has shown that greater activity is usually elicited by successful

[2] It is important to note that similar effects have also been observed in other aspects of the hippocampal formation, viz., in the parahippocampal cortex (Brewer et al., 1998; Davachi et al., 2003; Fernandez et al., 2002; Wagner et al., 1998) and in the entorhinal cortex (Cameron et al., 2001; Strange et al., 2002).

retrieval as opposed to unsuccessful retrieval (Kirwan & Stark, 2004; Stark & Okado, 2003; Stark & Squire, 2001). Expounding on this thought, Eldridge, Knowlton, Furmanski, Bookheimer, Engel, (2000) investigated episodic and non-episodic retrieval in 12 healthy participants. Results showed that hippocampal activity increased during retrieval that was accompanied by conscious recollection of learnt information, but that no such increases were evident when retrieval was based on the familiarity of the items. The authors suggest that hippocampus, therefore, selectively supports the retrieval of episodic memories.

Another line of research has implicated the hippocampus as being a structure critical to spatial memory and spatial cognitive processing. This research has sought to support theoretical claims that one of the more specific functions of the hippocampus lies in representing the spatial locations of an environment, and thereby playing a significant role in spatial orientation. More details regarding this domain of research are provided below. Before moving onto those details, however, it is useful to outline the way in which stress hormones (specifically, glucocorticoids) modulate hippocampal processing, and therefore how exposure to traumatic events may disrupt optimal hippocampal functioning.

The Hippocampus and Stress

As mentioned above, when an individual is exposed to a stressful situation, certain hormones are secreted; these in turn elicit particular behavioural responses. Studies investigating the influence of stress hormones on the hippocampus have suggested that damage to the structure is associated with its direct exposure to glucocorticoids (Sapolsky, Uno, Rebert, & Finch, 1990) and that prenatal exposure to elevated levels of glucocorticoids results in hippocampal damage (Uno et al., 1990, cited in Bremner, 1999).

As discussed above, intact hippocampal structure and optimal hippocampal functioning are required for the uninterrupted encoding, consolidation, and retrieval of episodic memories (Payne & Nadel, 2004; Squire, 1992). Logically, therefore, highly stressful or traumatic events place the individual at high risk for disrupted hippocampal functioning and consequent difficulties in memory processing.

A large body of empirical research supports this contention. For instance, animal studies have shown that rats exposed to the stress of an unfamiliar environment show deficits in working memory that are indicative of hippocampal dysfunction (Diamond et al., 1999). Other rat studies have shown that high levels of glucocorticoids associated with chronic stress affect spatial memory performance (Luine, Villages, Martinex, McEwen, & Bruce, 1994; Roozendaal, 2000; Roozendaal, Griffith, Buranday, de Quervain, & McGaugh, 2003). For

example, Diamond, Park, Heman, and Rose (1999) investigated the effects of predator exposure on hippocampal-dependent behaviour in rats trained in the radial arm water maze (RAWM). This study used a simple four-arm maze and a more complex six-arm maze. The rats learned the location of a hidden target and were subsequently placed in either a non-stressful environment (their home cage) or a stressful environment (in close proximity to a cat) for a 30-minute delay period, and then returned to the maze. Rats that were placed in the stressful environment showed impairments in locating the hidden target, compared to rats that were placed in their home cage, in the six-arm version of the RAWM. This suggests that stress does impact spatial memory performance.

Studies of human samples have produced data congruent with those reported above for animals. For instance, Lupien and colleagues (1997) subjected 14 healthy adults to a stressful task and discovered that, under these conditions, participants showed significantly decreased declarative memory performance in comparison to participants who had been exposed to a non-stressful condition. Furthermore, that study successfully demonstrated that (a) stress affects memory functions that are dependent on hippocampal activity, and (b) the stress-induced release of glucocorticoids contributes to this effect.

Laboratory studies such as those reviewed above have led many researchers to investigate possible hippocampal damage, and the consequent impairment on hippocampal-dependent cognitive tasks, caused by the increase in stress hormones during traumatic exposure in naturalistic situations. For instance, Bremner and colleagues (1997) conducted structural MRI scans on 17 survivors of childhood abuse, and discovered that patients with PTSD had a significantly lower left hippocampal volume than did control participants. Many other neuroimaging studies of PTSD have similarly found that hippocampal volume is significantly smaller in patients with PTSD (see, e.g., Bremner et al., 1998; Gilbertson et al., 2002; Gurvits et al., 1996; Villarreal et al., 2002).

By way of summary, two recent meta-analyses (Bremner, Noriyuki, Vaccarino, Kutner, & Weiss, 2005; Smith, 2005) confirmed that adults with PTSD have significantly smaller hippocampal volumes, bilaterally, than do those without PTSD. One of these meta-analyses (Bremner et al., 2005) reviewed nine studies featuring a total of 133 adult participants with chronic PTSD, 148 healthy controls, and 53 traumatized controls. The results showed that participants with chronic PTSD had significantly smaller volumes of both right and left hippocampi compared to participants in the other two groups.

Smith's (2005) meta-analysis of 13 studies confirmed these results. This meta-analysis included a total 215 adult patients with PTSD and 325 control participants. The reviewed

studies varied with respect to age, gender distribution, source of trauma, severity of symptoms, as well as the methods employed for volumetric quantification. Despite these differences, significant bilateral volume differences were evident. On average, participants with PTSD had a 6.9% smaller left hippocampal volume, and a 6.6% smaller right hippocampal volume.

In light of research suggesting that there is an association between naturalistic exposure to trauma (and, sometimes, consequent PTSD) and reduced hippocampal volume, one might assume that these structural changes may also be associated with changes in hippocampal-dependent cognitive functions. Indeed, many studies have indicated that naturalistic exposure to severe stress can impair human learning and memory (Bremner et al., 1993, 1995; Gilbertson et al., 2002).

Golier, Yehuda, Lupien, and Harvey (2003) investigated memory performance in 31 Holocaust survivors with PTSD, 16 Holocaust survivors without PTSD and a non-traumatised control group of 35 Jewish adults not exposed to the Holocaust. Memory was assessed using paired-associate recall (an explicit memory task) and word-stem completion (an implicit memory task). The results indicated markedly poorer explicit memory performance in the PTSD group, but no statistically significant between-group differences on the implicit memory task. Interestingly, the traumatised non-PTSD survivors did show implicit memory impairment relative to the healthy controls, but none of these differences were statistically significant (Golier et al., 2002).

The data from these studies are consistent with most of the neuropsychological research in this domain, which finds that deficits in verbal memory are associated with exposure to traumatic stress and with PTSD (Bremner, Vermetten, Afzal & Vythilingam, 2004; Shin, Rauch, & Pitman, 2006; Vasterling et al., 2002; Yasik, Saigh, Oberfield, & Halamandaris, 2007). In order to gain more insight into this association, the bilateral functionality of the hippocampus needs to be discussed.

The involvement of the left hemisphere hippocampal formation in verbal memory processing is well documented (Bell et al., 2002; Leritz, McGlinchey, Grande, Lundgren, & Milner, 2006). The involvement of the right hemisphere hippocampal formation in non-verbal (or, more specifically, spatial) memory processing is, however, equally well documented (Smith & Milner, 1981; Maguire, 1999; Roche, Mangaoang, Commins, & O'Mara, 2005). For instance, Maguire, Burgess, and O'Keefe (2002) reviewed neuropsychological, behavioural, and neuroimaging studies and concluded that whereas the right hippocampus seems to be involved in memory tasks requiring allocentric processing of

spatial locations, the left hippocampus seems to be involved in verbal episodic and autobiographical memory processing. Therefore, any damage done to the hippocampus bilaterally could lead to impairment in both verbal declarative memory and spatial cognition (Baddeley, Michael, Kopelman, & Wilson, 2002).

Few studies have, however, addressed the relationship between naturalistic exposure to traumatic stress, hippocampal damage, and impaired spatial learning and memory. The studies that have explored both verbal and non-verbal memory functioning (e.g., Bremner et al., 1995) have, by and large, reported the presence of deficits in the former but not in the latter. (It should be noted, however, that a few studies have reported that individuals exposed to traumatic events perform more poorly on visuo-spatial copying & visuo-constructional tasks in comparison to healthy matched controls (Emdad & Sondergaard, 2006; Gurvits et al., 2002). The details and implications of these studies will be discussed further in the introduction to Study 1.)

In summary, despite the known link between the right hemisphere hippocampus and spatial memory and learning, few studies have fully explored visuo-spatial dysfunction in participants who experienced early adverse life events. Hence, the studies reported here aimed to investigate memory problems that relate specifically to right hippocampal dysfunction. Before outlining the specific objectives of the current research, however, prior research describing the role of the hippocampus in spatial cognition will be reviewed.

The Hippocampus and Spatial Cognition

As mentioned above, the hippocampus is functionally associated with long-term declarative and episodic memory. It appears to be central to a neural system that encompasses both verbal (left hemisphere) and non-verbal/spatial (right hemisphere) learning processes and memory encoding and retrieval. As also noted above, the focus of the current research is on the functions of the right hemisphere hippocampus, and, in particular, on the role of that brain region in spatial cognition.

Researchers who study spatial cognition have identified that, in their day-to-day activities, humans use at least two kinds of navigation strategies. *Route following*, or landmark-guided navigation, involves following a familiar route in a stimulus-response fashion, where the person performs the task almost unconsciously (e.g., walking the same way from work to home every day). The other kind of navigation is a deliberate, consciously controlled process that depends on knowing spatial relations among various landmarks (e.g., trying to locate a new destination in a familiar environment). This form of navigation is

typically called *wayfinding*, or cognitive map-guided navigation (Maguire, Burgess, & O'Keefe, 1999; O'Keefe & Nadel, 1978; Tolman, 1973).

Navigation based on route following is thought to rely on the knowledge of places or landmarks and the routes that connect them. Route knowledge can therefore be thought of as a sequence of view-based (egocentric) visual images of landmarks together with directions. When exploring an environment from ground level without the help of a map, route knowledge is the type of navigation information that most people first acquire (Thorndyke & Hayes-Roth, 1982).

In contrast, navigation based on wayfinding or cognitive mapping is thought to rely on an understanding of the spatial relations between locations within an environment. This understanding can be referred to as survey knowledge. Survey representations provide an overview of the spatial layout, based on an extrinsic (allocentric) frame of reference. In general, the acquisition of survey knowledge appears desirable for successful and flexible orientation in an environment (Cornell & Heth, 2000; Munzer, Zimmer, Schwalm, Baus, & Aslan, 2006).

Wayfinding and route following are not only distinguishable in terms of the kinds of knowledge on which they are based; they are also neurally distinguishable. Studies involving rodents, and more recently humans, have shown that wayfinding and route following involve different forms of representation with correspondingly distinct neural bases (Bohbot, Iaria, & Petrides, 2004; Hartley, Maguire, Spiers, & Burgess, 2002; McNamara & Shelton, 2003; Mellet et al., 2000; Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe & Nadel, 1978). More specifically, a reasonably large body of literature has suggested that the right hemisphere hippocampus has a bias towards processing spatial relationships and has a special role in mapping large-scale space (see, e.g., Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Thomas, 2003; Worsley et al., 2001)

This cognitive mapping literature has its neural roots in a single study conducted almost 40 years ago. O'Keefe and Dostrovsky (1971) found that the firing of certain hippocampal cells in rats, termed "place cells", encodes the location of the animal; a unique place cell fires when the animal is within a particular portion of its environment. The orientation of the place cell representation is strongly modulated by landmarks in the environment (i.e., distal cues). Building on that finding, O'Keefe and Nadel (1978) set out the original version of cognitive mapping theory, which posited that a fundamental function of the hippocampus is the construction and maintenance of spatial maps of the environment.

Numerous studies have confirmed this hypothesis of location-specific activity in the hippocampal formation, and in particular within the hippocampus (McNaughton, Barnes, & O'Keefe, 1983; Muller & Kubie, 1987; Olton et al., 1978). Subsequent studies have also found that the activity in these place cells is independent of any particular stimulus, but reflects instead the existence and topography of multiple environmental cues (O'Keefe & Conway, 1978). Further, O'Keefe and Burgess (1996) illustrated that the shape and locus of place fields within a rectangular chamber are determined by the dimensions of the environment and by the spatial relations between walls of the environment.

Recent studies have revealed similar place-cell firings in humans. For example, Ekstrom et al. (2003) found evidence for neural correlates of human spatial navigation in hippocampal cells that fire in response to specific spatial locations. It is important to mention that this study also identified (a) cells in the parahippocampal gyrus that fire in response to views of landmarks, and (b) cells throughout the frontal and temporal lobes that respond to the subjects' navigational goals in relation to the environment.

Neural correlates of cognitive mapping have also been illustrated in lesion studies involving rats (Pearce, Good, Jones, & McGregor, 2004; Pearce, Roberts, & Good, 1998) and humans (Bohbot, Allen, & Nadel, 2000). Pearce et al. (1998) found that hippocampal lesions in rats disrupted spatial navigation based on cognitive maps. This study showed evidence of different neural networks being activated when different spatial strategies are employed. Bohbot et al. (2000) replicated this finding in humans. They administered spatial and nonspatial memory tasks to patients with small thermal lesions in the medial temporal lobes. Patients with lesions in the right hippocampus showed deficits specifically relating to visual-spatial memory, whereas patients with lesions in the left hippocampus showed deficits relating to verbal-declarative memory.

Two recent fMRI studies have provided even more convergent data suggesting that the right hemisphere hippocampus is central to cognitive mapping. Bohbot and Iaria (2004) compared the virtual environment navigation performance of 15 patients with unilateral medial temporal lobe lesions (11 with right medial temporal lesions) to that of 10 age-, education-, and gender-matched healthy controls. The study investigated two independent navigational strategy systems: a spatial strategy based on the use of multiple landmarks in the environment, and a response strategy that required utilisation of a learnt route involving right and left turns from a given starting location. The fMRI analysis of the control group was used to assess which neural regions were activated during which tasks. This analysis indicated that the use of a spatial strategy was associated with significant activity in the right hippocampus,

whereas the use of a response strategy was associated with sustained activity in the caudate nucleus. Behavioural analysis showed that, as expected, participants in the lesion group made significantly more errors on tasks involving the spatial strategy, to the extent that more than half of the patients using the spatial strategy shifted to use a more nonspatial strategy.

Similarly, Kumaran and Maguire (2005) compared patterns of brain activation while their participants (18 healthy individuals) performed two tasks placing similar demands on relational processing: navigation within either a spatial domain (their city) or a non-spatial domain (their social network). They showed that execution of these two complex tasks resulted in very different patterns of brain activation; specifically, the right hippocampal regions were engaged by relational processing in a spatial (city), but not in a non-spatial (social), domain.

Numerous studies have also explored the role of other medial temporal lobe structures in spatial navigation. Much of this research points to the parahippocampal gyrus as being associated with exploring and learning the topography of a three-dimensional environment. For instance, Aguirre, Detre, Alsop, and D'Esposito (1996) examined the contributions of medial temporal structures in nine right-handed males during the topographic learning of a virtual maze. Increased activity was evidenced in the parahippocampus during the learning and recall of topographic information.

Similarly, Mellet et al. (2000) analysed the fMRI results of five healthy right-handed participants during the mental exploration of an environment learned from actual navigation. The parahippocampal gyrus bilaterally, in addition to the right hippocampus, was activated during this task. The authors suggest that this bilateral activation of the parahippocampus is involved when the environment incorporates route information and object landmarks.

Another fMRI study focussing on the neural distinction between wayfinding and route following found greater activity in the posterior parahippocampal gyrus was associated with the former in contrast to the latter. The same study found that activity in the hippocampal region was correlated with the accuracy of the participants' performance (Hartley et al., 2003).

Taken together, the evidence from this group of studies suggests that, in humans, (a) the hippocampus is preferentially engaged during cognitive mapping tasks, and (b) spatial navigation/cognitive mapping is not necessarily hippocampus-specific, but rather that the structure forms a critical part of a large network dedicated to spatial cognition (Maguire, Burgess, & O'Keefe, 1999).

With regard to this neural network, Burgess, Maguire, Spiers, and O'Keefe (2001) used a virtual environment and fMRI to investigate brain regions involved in remembering the spatial context of life-like events. The study involved 13 healthy male volunteers receiving objects from two different people in two different places within the virtual environment. Memory retrieval was assessed by placing the participants back in the company of a person and giving them a forced choice of objects. A network of areas, consisting of a temporoparietal pathway running between the precuneus and the parahippocampi via other neural structures including the left hippocampus, the dorsolateral, ventrolateral and anterior PFCs and the ACC, was found to be involved in this task. Based on these data, the authors suggested that the parahippocampus is heavily involved in the retrieval of spatial context, and that the prefrontal activations were associated with strategic retrieval processes. The authors suggest that the activation in the left hippocampus is possibly associated to a retrieval of the context of an event from long-term memory. An adjusted threshold also showed activation in the right hippocampus, which, because of its involvement in visual spatial memory, is associated with performance in these navigation tasks.

Specific Objectives of the Current Research

From the literature reviewed above it is clear that neurobiological responses to stressful situations involve a number of brain regions, and affect the functionality of many of these regions. Although the body of research into the associations between traumatic stress and brain structure and function is large and constantly expanding, much remains unknown about the exact nature of the cognitive deficits in individuals with a history of trauma exposure. The aim of this study is to contribute to the literature describing the relationships, and mechanisms of association, between adverse childhood events and adult neurocognitive impairment. Specifically, the studies reported here seek to fill a gap in the literature by investigating visual-spatial memory and cognitive mapping/wayfinding in individuals with a history of childhood trauma.

The current research comprises two separate studies. Study 1 investigated whether young adults with a history of childhood trauma performed differently to healthy matched controls on a set of visual-spatial memory tasks. Study 2, used fMRI techniques to investigate whether any differences in neural activation would be evident, in individuals with a history of childhood trauma, during spatial navigation tasks.

Study 1: Visual-Spatial Memory in Adults with Childhood Traumatic Experiences

Introduction

The literature reviewed above makes it clear that, although research into the associations between traumatic stress and cognitive function is growing, much remains unknown about the nature of the cognitive deficits in individuals who have experienced traumatic events. For instance, few studies have fully explored visual-spatial memory in people who have experienced early adverse life events.

Although many studies have reported that memory dysfunction is associated with the experience of a traumatic stressor, most have noted impairments in only verbal declarative memory (Bremner, Vermetten, Afzal, & Vythilingam, 2004; Gilbertson et al., 2002; Golier et al., 2002; Shin, Rauch, & Pitman, 2006; Vasterling et al., 2002; Yasik, Saigh, Oberfield, & Halamandaris, 2007). The few studies that have also investigated visual memory processes in traumatised individuals have reported inconsistent results.

For instance, Bremner et al. (1995) found that adult survivors of childhood abuse performed more poorly than age-, education-, and IQ-matched controls on measures of verbal short-term memory, but not on measures of visual short-term memory. The visual memory measures used in this study were Figural Memory, a subtest of the Wechsler Memory Scale (WMS; Russell, 1975), and the Visual Selective Reminding Procedure (ViSRT; Buschke & Fuld, 1974; Hannay & Levin, 1985). It is important to note that these measures do not necessarily tap hippocampal function, which, as mentioned before, is a region directly affected by stressful situations (Bremner, Noriyuki, Vaccarino, Kutner, & Weiss, 2005; Sapolsky, Uno, Rebert, & Finch, 1990; Smith, 2005).

In contrast to Bremner et al. (1995), Emdad and Sondergaard (2006) found that male adult PTSD patients performed more poorly than age-, education-, and ethnicity-matched healthy controls on a measure of visuo-constructional ability (Block Design Test; Koh, 1923). Similarly, Gurvits et al. (2002) found that individuals diagnosed with PTSD showed impaired visuospatial copying abilities relative to trauma-exposed non-PTSD individuals. These latter two studies used tests of visuospatial abilities that had no memory component; therefore, it can be assumed that these tests do were more likely to tap right parietal, rather than right hippocampal, function. Emdad and Sondergaard (2006) and Gurvits et al. (2002) also assessed participants who were exposed to traumatic events in adulthood. As mentioned above, exposure to severe stress and trauma early in life may set in motion neurobiological

events that can cause significant and lasting changes in brain development (Vasterling & Brewin, 2005). These changes can, in turn, have a significant negative impact on cognitive functioning in adulthood. It is therefore expected that stressful situations that occur during neuronal development (i.e., in childhood) might have a greater and more lasting impact on the brain circuitry of an individual compared to traumatic situations that occur in adulthood.

Many trauma studies have shown the hippocampus and PFC, and their associated functions, to be affected by stressful situations (Bremner, 2001; Carrion, Weems, & Reiss; 2007; Lupien et al., 1994; McLaughlin, Gomez, Baran, & Conrad, 2007; Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Newcomer et al., 1999). As mentioned above, however, few have investigated visual-spatial memory in adult survivors of childhood trauma. This, coupled with the fact that lesion studies have shown spatial cognitive impairments in animals and humans with temporal lobe lesions (Bohbot, Allen, & Nadel, 2000; Pearce, Good, Jones & McGregor, 2004; Pearce, Roberts, & Good, 1998), indicates that more research is needed to explore the relationship between childhood trauma and adult visual-spatial memory.

The aim of this study, then, was to investigate visual-spatial memory functioning in adults who had experienced a traumatic childhood event. The following hypothesis was tested: Participants with a history of childhood trauma will perform more poorly on neuropsychological tests of visual-spatial memory than will healthy control participants.

Method

Participants and Procedure

As depicted by Figure 1, 856 adults between the ages of 18 and 28, primarily from the University of Cape Town's student population and surrounding community, were recruited into a large study of childhood trauma and its consequences. Posters advertising the research were placed in and around most departments on campus, as well as in student residences and on public notice boards. The posters directed interested individuals to an online survey that acted as an initial screening procedure. The Figure further illustrates the flow of participants through the various stages of Study 1 and Study 2.

Individuals who completed the survey were excluded from further participation in the research reported here if their self-rating on the Edinburgh Handedness Scale (Oldfield, 1971) suggested that they were primarily left-handed. Only right-handed participants were included in the study in order to eliminate the possibility of individual differences in cerebral functional organization. Thirty-nine individuals who completed the survey were excluded from further participation on this basis.

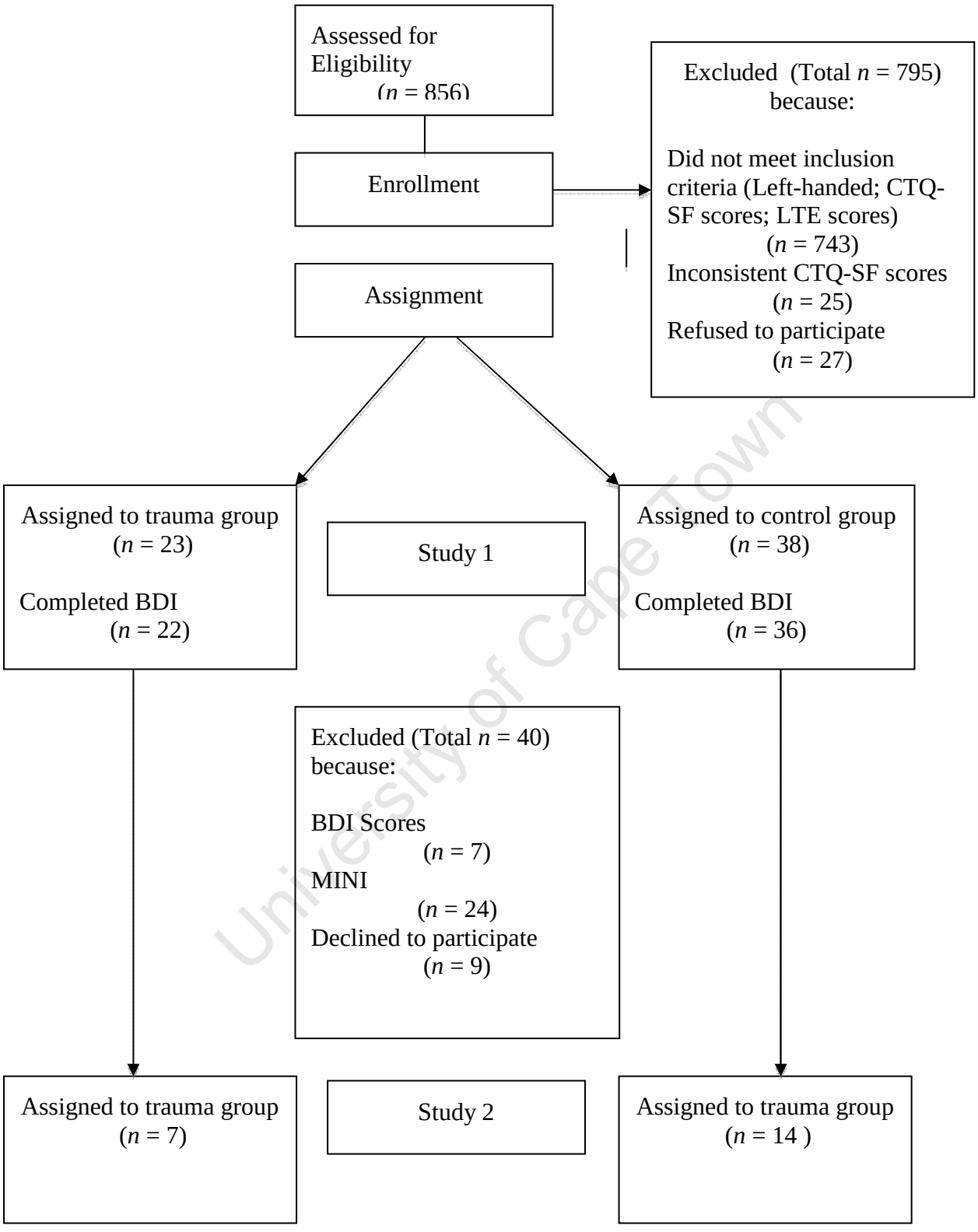

Figure 1. Flow of participants through each stage of the study

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

Individuals who completed the survey but who obtained high scores on the Minimalization/Denial subscale of the Childhood Trauma Questionnaire – Short Form (CTQ-SF; Bernstein & Fink, 1998) were excluded from further participation. This sampling criterion was put in place because the CTQ-SF was the only measure of childhood trauma used in this study, and therefore it was essential to exclude all questionable CTQ profiles. Twenty-three individuals who completed the survey were excluded from further participation on this basis.

Finally, individuals who completed the survey but who obtained a low to moderate score on 2 or more subscales of the CTQ-SF (see Appendix A), and did not have at least one moderate to severe score on at least one CTQ-SF subscale, were excluded from further participation. Six hundred and seventy individuals who completed the survey were excluded from further participation on this basis. This latter sampling criterion was put in place to help ensure that we could establish two clearly defined groups:

1. A Control group (n = 68), consisting of individuals with either (a) scores in the minimal range on all CTQ-SF subscales, or (b) a score in the low to moderate range on only one CTQ-SF subscale
2. A Trauma group (n = 45), consisting of individuals with a score in the moderate to severe range on at least one CTQ-SF subscale.

In summary, after analyzing the data derived from the online survey, 113 of the 856 individuals who had completed the survey were deemed eligible to continue participation in the research reported here. These individuals were contacted and invited to an in-person interview and testing session. At this stage of the study, 27 individuals either declined to participate further[3] or were unreachable.

This interview and testing session was conducted in the Applied Cognitive Science and Experimental Neuropsychology Team (ACSENT) laboratory in the UCT Department of

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

Psychology. The participants were asked to fill out another CTQ-SF, as well as a questionnaire relating to depressive symptomatology (the Beck Depression Inventory-II (BDI-II); Beck, Steer, & Brown, 1996). Those with CTQ-SF scores that were inconsistent across the online and in-person administrations (i.e., those whose trauma status differed between the first and second CTQ-SF self-reports) were excluded from further participation. On this basis, we excluded 25 participants (16 from the Control group and nine from the Trauma group).

Therefore, after this initial screening phase of the in-person interview and testing session, 61 individuals were determined to be eligible for the continued participation. The demographic and clinical profiles of those participants are presented in Table 1.

Demographic and Clinical Characteristics of the Study 1 Sample (N = 61)

Table 1.

Demographic and Clinical Characteristics of the Study 1 Sample (N = 61)

	Trauma (n = 23)	Control (n = 38)	t^a / χ^2	p	Cohen's d
Age	21.04 (3.57)	22.97 (13.02)	-0.71	0.487	-0.20
Sex (M:F)	7:16	16:22	0.83[b]	0.358	---
CTQ-SF					
Sexual Abuse	7.26 (2.98)	5.12 (0.45)	3.32	< .001***	1.00
Physical Abuse	8.52 (3.03)	5.47 (0.76)	4.74	< .001***	1.38
Emotional Abuse	12.39 (5.26)	6.42 (1.33)	5.26	< .001***	1.56
Physical Neglect	7.70 (2.74)	5.42 (1.00)	3.83	< .001***	1.11
Emotional Neglect	13.22 (5.25)	7.32 (2.14)	5.14	< .001***	1.47
BDI-II	10.82 (9.03)	5.06 (4.63)	2.78	< .001***	0.80

Note. Means are presented with standard deviations in parentheses. CTQ-SF = Childhood Trauma Questionnaire – Short Form; BDI-II = Beck Depression Inventory II.
[a]All *t*-tests are 1-tailed, calculated with separate variance estimates.
[b]Results of chi-square analysis.
*p < .05, **p < .01, ***p < .001

As the Table shows, there were no statistically significant between-group differences with regard to age or to male: female ratio. With regard to another important demographic variable, education, all participants in this sample were members of the UCT student population, and therefore it can be assumed that there were no statistically significant between-group differences in this regard. As expected given the study's inclusion criteria, there were statistically significant between-group differences on all CTQ-SF measures.

Finally, all 61 participants completed a battery of four subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Fray, Robbins, & Sahakian, 1996). Three of these tests measured aspects of visual-spatial memory that are hippocampal-dependent (Sahakian et al., 1988), while one (Spatial Recognition Memory) measured a cognitive process (spatial working memory) that relies on frontal aspects of working memory. All of these tests made use of the Cambridge Cognition touch screen apparatus, and they are all described in detail below.

Materials

Childhood Trauma Questionnaire – Short Form (CTQ-SF). The CTQ-SF (Bernstein & Fink, 1998) is a retrospective self-report instrument that is a reliable and valid measure of childhood neglect or abuse. It contains five subscales, three assessing abuse (Emotional Abuse, Physical Abuse, and Sexual Abuse) and two assessing neglect (Emotional Neglect and Physical Neglect). Respondents are required to rate the extent to which they experienced different traumatic childhood events. Each subscale consists of 5 items; participants have to respond to each of them on a 5-point Likert-type scale, ranging from "never true" to "very often true". The minimum score of 5 on a particular subscale indicates no history of abuse or neglect, while the maximum score of 25 indicates an extreme history of abuse or neglect. The instrument also contains a three-item Minimization-Denial subscale to help detect false-negative trauma reports.

The CTQ-SF has demonstrated excellent test-retest reliability, convergent validity, and discriminant validity with therapists' independent ratings of child abuse (Bernstein et al., 2003). It was suitable for the purpose of the current study as it is brief (it can be administered in only 5 minutes) and appropriate for use in the target population (Raudsepp, 2006). The CTQ-SF has been used successfully in previous trauma research in South Africa (Lochner et al., 2004).

Edinburgh Handedness Inventory. This instrument is a self-report measure of hand preference (Oldfield, 1971). The respondent is required to indicate which hand he/she would

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

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

Beck Depression Inventory – Second Edition (BDI-II). The BDI-II (Beck, et al., 1996) assesses current presence and severity of depressive symptoms. The instrument adheres closely to the DSM-IV diagnostic criteria for MDD and could be reliably used in the target sample as it has been specifically designed to assess depression in adults and adolescents of or above the age of 13 years (Whisman, Perez, & Ramel, 2000). Each of the 21 BDI-II items corresponds to a specific category of depressive symptom and/or attitude, and each consists of a graded series of four self-evaluative statements. Respondents are required to consider how each statement relates to the way they have felt in the past 2 weeks. The BDI-II has achieved adequate reliability and validity for use in both clinical and research settings (Beck et al., 1996; Whisman et al., 2000). It is regularly used in South African research studies (e.g., Ward, Flisher, Zissis, Muller, & Lombard, 2001).

CANTAB Delayed Matching to Sample (DMS). This subtest assesses forced-choice recognition memory for novel non-verbalisable patterns, and tests short-term visual memory. Performance on this task has been associated with activation in the medial temporal lobes, with some input from the frontal lobes (Hampson, Heyser, & Deadwyler, 1993; Stern, Sherman, Kirchhoff, & Hasselmo, 2001).

During the DMS learning phase, a block containing a complex visual pattern is presented in the middle of the screen. While that pattern is being displayed, the participant is presented simultaneously with four different complex visual patterns, one of which matches

the target pattern. The participant is required to indicate, by touching the appropriate pattern, which of the four possible choices exactly matches the sample. Once this simultaneous trial has been completed successfully, another complex visual pattern is presented in the centre of the screen. After a few seconds the pattern disappears and immediately four different complex visual patterns are presented. The participant must then again select the correct option. Once this 0-second delay trial has been completed successfully, another complex visual pattern is presented in the centre of the screen. After a few seconds this pattern disappears, and after 12 seconds the participant is presented with a set of response options as in the previous trials. The learning phase concludes once the participant has completed this 12-second delay trial successfully.

After the learning phase is completed, the participant is required to complete two test blocks of 20 trials. Each block consists of five simultaneous trials, five 0-second delay trials, five 4-second delay trials, and five 12-second delay trials. Types of trials are randomised within the blocks. The DMS subtest takes approximately 10 minutes to complete.

CANTAB Paired Associates Learning (PAL). This subtest assesses new learning and memory in the visual modality; performance is sensitive to changes in medial temporal lobe functioning (Sahakian & Owen, 1992).

In this subtest, square white boxes are displayed on the borders of the screen and are opened and closed in a randomised order. One or more of them contains a pattern. Once all the boxes have been opened and closed, the patterns that were in the boxes are then displayed in the middle of the screen, one at a time. As each pattern is displayed, the participant is required to touch the box in which the pattern was originally located. If the participant makes an error, all the patterns are re-presented to remind him/her of their locations.

The PAL subtest consists of eight trials, which increase in difficultly as the task progresses. The first seven trials feature six white boxes, while the eighth features eight such boxes. One pattern is displayed in the first two trials, two are displayed in the third and fourth trials, three are displayed in the fifth and sixth trials, six are displayed in the seventh trial, and eight are displayed in the eighth stage. The PAL subtest takes approximately 10 minutes to complete.

CANTAB Pattern Recognition Memory (PRM). This subtest assesses visual pattern recognition memory in a 2-choice forced discrimination paradigm. This task is also sensitive to dysfunction in the medial temporal lobes, but is relatively insensitive to dysfunction in the frontal lobes (Sahakian & Owen, 1992).

In the presentation phase of this subtest, the participant is shown a series of 12 visual patterns, one at a time, in the centre of the screen. These patterns are designed so that they cannot easily be given verbal labels. In the recognition phase, the subject is presented with two patterns (a target (one of the 12 patterns displayed previously) and a distracter), and is required to select the one that was displayed previously. In the recognition phase, the patterns are presented in reverse order from the one in which they appeared in the presentation phase (i.e., the 12^{th} pattern in the presentation phase is presented first in the recognition phase, while the first pattern in the presentation phase is presented last in the recognition phase). This task is repeated twice (with 12 different patterns), and can be completed in approximately 5 minutes.

CANTAB Spatial Recognition Memory (SRM). This is a test of visual-spatial recognition memory in a 2-choice forced discrimination paradigm. This test is primarily sensitive to dysfunction in the frontal lobes, while being relatively insensitive to temporal lobe abnormalities (Sahakian & Owen, 1992). In the current research, it therefore was useful in dissociating frontal memory functions from medial temporal lobe memory functions.

In the presentation phase of this subtest, a white square appears in sequence at five different locations on the screen. In the recognition phase, the subject sees a series of five pairs of squares, one of which is in a place previously seen in the presentation phase while the other is a distractor square in a location not seen in the presentation phase. As with the PRM test, locations are tested in the reverse of the presentation order. This subtest consists of four such trials, each time with the five squares presented in five different locations, and takes approximately 5 minutes to complete.

Statistical Analysis

The CANTAB software produced an output file containing the scores of each participant for several outcome variables across each of the four subtests. The following outcome variables were deemed most relevant for the current study:

1. The DMS percent correct (all delays) outcome variable reports the number of occasions the participant selected the correct stimulus in trials when the target stimulus and the three distractors were presented after the stimulus had been hidden, with delays of 0-s, 4-s, and 12-s. The DMS percent correct (simultaneous) outcome variable reports the number of occasions that the correct target is selected, when target is not hidden and the four options are presented simultaneously to the participants. The *a priori* predictions for this test were that there would be no

statistically significant between-group performance differences on the simultaneous task, but that there would be such differences across the delay tasks.

2. The PAL (total errors adjusted) outcome variable reports the total number of errors on this subtest, with an adjustment for each stage not attempted due to a previous failure. The *a priori* prediction here was that participants in the Trauma group would make statistically significantly more errors than those in the Control group.
3. The PRM percentage correct outcome variable reports the percentage of correct choices made by the participants in this task. The *a priori* prediction for this test was that participants in the Trauma group would make statistically significantly fewer correct choices than participants in the Control group.
4. The SRM percentage correct outcome variable reports the percentage of correct squares chosen by the participants in this task. Because this is a non-hippocampal dependent test, the *a priori* prediction for this test was that there would be no statistically significant between-group differences on this task.

All statistical analyses were conducted using the software packages Statistica version 7 (StatSoft, 2004) and SPSS version 15.0 (SPSS Inc., Chicago, IL). The threshold for statistical significance was set at $\alpha = 0.05$. Details of each individual analysis are given within the Results section.

The achieved power is 0.59 for a one-tailed *t*-test, given the current sample size and alpha level and a medium effect size ($d = 0.5$). With a small effect size ($d = 0.2$), the achieved power is 0.19; with a large effect size ($d = 0.8$), the achieved power is 0.91.

Results

Testing assumptions underlying inferential statistics. Table 2 presents descriptive statistics for all of the CANTAB data. The data generally met the assumptions for *t*-tests of independent samples. More specifically, the research design meant that the groups were unrelated and subjects were independently and randomly sampled from the population of interest. Furthermore, normal probability plots indicated that the data were normally distributed (See Appendix B). Finally, as shown in Table 2, Levene's test for homogeneity of variance was not statistically significant for the DMS percent correct (all delays), the PRM, and the SRM outcome variables. Levene's test was statistically significant for DMS percent correct (simultaneous) and PAL total errors (adjusted) outcome variables. In the latter cases, separate variances estimates were taken and *t*-tests then conducted.

Between Group Comparisons. Table 2 also presents the results of between-group comparisons of performance on all of the CANTAB outcome variables. With regard to DMS subtest trials where there was a delay between target and choice presentation, participants in the Control group selected the correct stimulus statistically significantly more often than did those in the Trauma group. In contrast, when the target and choices were presented simultaneously, there were no statistically significant between-group differences. Both of these results confirm the *a priori* predictions. The effect sizes for this task suggest a relationship of medium strength.

With regard to the PAL subtest, participants in the Trauma group made statistically significantly more total errors than did those in the Control group, and analysis showed a large effect size. These data, then, also confirm the *a priori* prediction.

With regard to the PRM subtest, there were no statistically significant between-group differences, and a small effect size was evident. These data, of course, do not confirm the *a priori* prediction.

With regard to SRM subtests, there were also no statistically significant between-group differences, and a small effect size was evident. These data therefore confirm the *a priori* prediction.

Analyses of covariance (ANCOVAs). As shown in Table 3, participants in the Trauma group also scored statistically significantly higher than those in the Control group on the BDI-II; this result suggests that, in this sample, childhood trauma exposure is associated with adult depression. Analysis of covariance was therefore conducted to investigate the impact the BDI scores had on the results of the CANTAB, specifically on those outcome variables on which statistically significant between-group differences had previously been detected (viz., DMS percent correct (all delays) and the PAL total errors (adjusted)). Table 3 shows the results of these two ANCOVAs. Even when BDI-II scores were controlled for, the data still indicate statistically significant between-group differences on these two outcome variables (and, in fact, controlling for BDI-II scores increased the significance on the DMS outcome variable). The BDI-II also showed almost no correlation with DMS outcomes (r = 0.05, p = 0.685) or with PAL outcomes (r = 0.03, p = 0.851).

However, the effect sizes went from being in the medium range to being quite small, suggesting that when BDI-II scores were controlled for, the amount of variance, that trauma status contributes to performance on these tasks, diminishes somewhat. This indicates that although BDI-II scores did not have a statistically significant impact on the outcomes of the task, they do have some influence on the strength of the results.

Discussion

A battery of CANTAB subtests was used to investigate whether there were any performance differences in visual-spatial memory between participants who had experienced a childhood trauma and healthy matched controls. The *a priori* predictions were that the Trauma group would perform, on average, more poorly than the healthy controls on the all of the CANTAB outcome variables barring the DMS percent correct (simultaneous trials) and the SRM (percent correct). Additionally, the expectation was that, because the participants in the Trauma group did not have PTSD and were reasonably high-functioning individuals drawn from a university student population, any deficits in their visual-spatial memory would not be as pronounced as if they had developed a post-traumatic psychopathology (Shin et al., 2004; Vasterling et al., 2002). The obtained data largely confirmed the *a priori* hypotheses: participants in the Trauma group showed relative impairments on two hippocampal-dependent subtests (a delayed matching to sample task and on a paired-associates learning task), but not on a frontal lobe-dependent subtest (a spatial working memory task).

The delayed matching to sample task (the CANTAB DMS subtest) specifically assesses recognition memory for novel non-verbalisable patterns, and tests both simultaneous and short-term visual memory. The neural correlates of this functionality are located in the medial temporal lobes, and, to a lesser extent, in the frontal lobes (Hampson, Heyser, & Deadwyler; 1993; Stern, Sherman, Kirchhoff, & Hasselmo, 2001). The finding that participants in the Trauma group performed more poorly than those in the Control group on this task is consistent with studies that have implicated both the hippocampal formation and the PFC, and their associated functions, as regions affected by stressful life events (Bremner, 2001; Carrion, et al., 2007; Kitayama, et al., 2006; Lupien et al., 1994; McLaughlin, et al., 2007; Newcomer et al., 1999; Vasterling & Brewin, 2005). Of special interest in this study, however, is that the Trauma group participants were not carrying a diagnosis of PTSD and yet still displayed dysfunctional responses compared to the controls. This suggests that visual-spatial memory is disrupted by exposure to traumatic events, and not specifically by the development of post-traumatic psychopathology.

The paired-associates learning task (the CANTAB PAL subtest) is specifically designed to test visual memory and new learning for visual material. The neural correlates of this functionality are located primarily in the medial temporal lobes (Sahakian & Owen, 1992). On this task, participants in the Trauma group made significantly more errors than did participants in the Control group. The hippocampus and the PFC are often associated with the acquisition of new memories and with attentional control (Davachi et al., 2003; Davachi &

Wagner, 2002; Kirwan & Stark, 2004; MacDonald, Cohen, Stenger, & Carter, 2000; Reber et al., 2002), both of which are required for the successful completion of this task.

Taken together, the findings from the CANTAB DMS and PAL subtests suggest that individuals with a history of childhood trauma may experience mild impairment in cognitive domains subserved by dysfunctions hippocampal and PFC regions. These results are consistent with studies that have shown the structure of these brain regions to be affected by traumatic experiences (DeQuervain et al., 2003; Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Southwick, Yehuda, & Morgan, 1995; Vasterling, & Brewin, 2005).

The data revealed no between-group differences on both the PRM and the SRM subtests. The PRM specifically assess pattern recognition memory and is sensitive to dysfunction in the medial temporal lobes, but is relatively insensitive to dysfunction in the frontal lobes, while the SRM assesses visual-spatial recognition memory and is sensitive to dysfunction in the frontal lobes, but insensitive to temporal lobe abnormalities. With regard to the PRM, this result was unexpected. The pattern of data may be accounted for by the fact that the PRM task is much simpler to solve than either the DMS or the PAL (in fact, in many clinical situations the PRM is used as training for the PAL). Therefore, visual-spatial memory functioning in the Trauma group participants may be intact at a basic level, with disruptions only becoming evident when more complex tasks are presented.

With regard to the SRM, the pattern of data followed a priori predictions. No statistically significant between-group differences were expected because this task does not rely heavily on hippocampal activation. This suggests that there is no difference in PFC functioning in traumatised individuals, in simple working memory tasks.

From the results of the CANTAB, it would appear that in tasks which require activations from both the hippocampus and the PFC, the trauma group shows poorer performance, compared to the controls, however in simple tasks that require activation from only one of these regions they perform as well as the controls.

Taken together, the data presented above imply that deficits in the Trauma group participants do not reflect damage to individual brain regions, but rather reflect the disruption of a network involved in memory acquisition. Previous research has shown that the acquisition of memories involves a neural network that includes regions of the hippocampal formation (viz., the hippocampus, the parahippocampal gyrus, and the entorhinal cortex), and regions of the PFC (viz., the anterior cingulate cortex (ACC) and the dorsolateral PFC; Anderson et al., 2007; Fuster, 1997; Stern, Sherman, Kirchhoff, & Hasselmo, 2001). More complex tasks require a greater utilisation of this network, whereas simpler tasks require

input from fewer regions (Sahakian & Owen, 1992). For instance, more complex tasks may require an individual to recruit more attentional and working memory systems (located in the PFC), as well as medial temporal lobe systems, in order to successfully encode information (Davachi & Wagner, 2002; Kirwan & Stark, 2004; MacDonald, Cohen, Stenger, & Carter, 2000; Reber et al., 2002). In contrast, simpler tasks may only require input from specific regions (Sahakian & Owen, 1992).

This argument is further bolstered by the fact that this memory network is the same one that has been associated with disturbances caused by traumatic stress. Studies in PTSD have identified a network, including the hippocampal formation and the PFC, which is sensitive to traumatic exposure (Bryant et al., 2005; Elzinga & Bremner, 2000). This information, taken together with the results of the CANTAB, confirms that traumatised individuals seem exhibit dysfunctions in this entire network.

As previous research has indicated a strong association between traumatic exposure and depressive symptomology (Breslau, Davis, Peterson, & Schultz, 2000; Schnurr, & Green, 2004; Shalev et al., 1998), depression was controlled for in this study. As the results indicate, the BDI scores of our participants made little impact on the outcomes, but it must be mentioned that, when controlled for a more significant relationship was evidenced in certain tasks (e.g. DMS percent correct (all delays)). However, when the BDI scores were controlled for, the effect size diminished somewhat, suggesting that depression did have some influence on the strength of outcomes of the tasks.

In summary, the results of this study support the contention that young adults with exposure to early adversity (in the form of childhood physical, emotional, and sexual abuse and neglect) present with mild impairments in visual-spatial memory. Further, the results obtained here are consistent with the notion that the mechanism underlying these impairments in visual-spatial memory might be stress-related damage to specific brain regions (viz., the hippocampus and the PFC). In Study 2, the neural correlates of spatial cognition are further explored by the use of an fMRI paradigm.

Table 2.

Between-Group Comparison of Performances on the CANTAB Visual-Spatial Memory Battery

Subtest and Outcome Variable	Group: Trauma (n = 23)	Group: Control (n = 38)	Levene's p	t	p	Cohen's d
DMS						
% correct (all delays)	89.71 (7.17)	92.46 (5.18)	0.269	-1.73	0.044*	-0.44
% correct (simultaneous)[a]	99.57 (2.09)	98.16 (4.57)	0.004	1.64	0.107	0.40
PAL						
Total errors (adjusted)	4.87 (3.81)	2.87 (2.76)	0.011	2.19	0.011*	0.60
PRM % correct	93.3 (5.72)	92.87 (6.41)	0.594	0.26	0.398	0.07
SRM % correct	85.65 (8.16)	86.7 (8.4)	0.970	-0.48	0.316	-0.13

Note. In the second and third columns, means are presented with standard deviations in parentheses. DMS = Delayed Matching to Sample; PAL = Paired Associates Learning; PRM = Paired Recognition Memory; SRM = Spatial Recognition Memory. All *t*-tests were 1-tailed and calculated with separate variance estimates unless indicated otherwise.

[a]2 tailed *t*-test, calculated with pooled variance estimates; no differences between groups expected.

*$p < 0.05$, **$p < 0.01$, ***$p < .001$

Table 3.

Summary of ANCOVA Results for DMS Percent Correct (All Delays) and PAL Total Errors (Adjusted) with BDI-II Scores as a Covariate

	Group		Adjusted Means					
Subtest and Outcome Variable	Trauma (n = 23)	Control (n = 38)	Trauma (n = 23)	Control (n = 38)	Levene's p	F	p	η^2
BDI-II	10.82 (9.03)	5.06 (4.63)	----	----	0.876	1.71	0.197	0.04
DMS								
% correct (all delays)	89.71 (7.17)	92.46 (5.18)	88.83 (1.35)	92.94 (1.03)	0.208	5.42	0.024	0.09
PAL								
Total errors (adjusted)	4.87 (3.81)	2.87 (2.76)	5.11 (0.72)	2.60 (0.55)	0.010	7.17	0.010	0.12

Note. In the second and third columns, means are presented with standard deviations in parentheses. In the fourth and fifth columns, means are presented with standard error in parentheses. BDI-II = Beck Depression Inventory – Second Edition; DMS = Delayed Matching to Sample; PAL = Paired Associates Learning.

Study 2: Wayfinding in Adults with Childhood Traumatic Experiences: An fMRI Investigation

Introduction

The literature reviewed in the General Introduction makes it clear that, despite the large and ever-growing body of research into the associations between traumatic stress and hippocampal and PFC structure and function (Bremner, 2001; Carrion, et al., 2007; Kitayama, et al., 2006; MacDonald, et al., 2000; Sapolsky, et al., 1990), much remains unknown about the nature of the cognitive deficits in adults with early childhood adversity and about the contributions of putative hippocampal and ACC atrophy to those deficits.

Although many structural MRI studies have shown atrophy in both the hippocampus (Bremner et al., 1998; Bremner, et al., 2005; Gilbertson, et al., 2002; Gurvits et al., 1996; Smith, 2005; Villarreal et al., 2002) and the ACC (Kitayama, et al., 2006; Woodward, 2005) in individuals with a history of trauma exposure, not many of those neuroimaging studies have involved a functional component. The fact that no fMRI studies have involved a traumatised non-PTSD group, nor have any involved tasks which tap hippocampal & PFC functioning, in any trauma-exposed individuals, points to a gap in the literature that needs investigation.

A functional imaging component is, therefore, important in revealing the extent to which traumatic childhood events influence the functionality of these brain regions and networks.

Study 1 illustrated that traumatised non-PTSD individuals perform more poorly than matched controls on complex visual-spatial memory tasks. These data suggest that a disruption in the visual-spatial neural network (including, critically, the hippocampus and the PFC) may have occurred in adults who have experienced childhood trauma. Much research has also implicated these regions in spatial navigation; the hippocampus, in particular, is a structure central to cognitive mapping and wayfinding (Bohbot et al., 2000; Bohbot, Iaria & Petrides, 2004; Kumaran & Maguire, 2005).

Therefore, the aim of this study was to use fMRI to investigate the associations between childhood trauma, neural activation in brain regions that are typically affected by stress and trauma (i.e., the hippocampus and the PFC), and spatial navigation. In other words, unlike previous studies, the current research will consider functional, rather than volumetric, differences between participants with a history of trauma exposure and those with no such

history. The following specific hypotheses were tested: (a) Participants with a history of childhood trauma will, at a behavioural level, perform more poorly on spatial navigational tasks than will healthy control participants with no history of childhood trauma; and (b) participants with a history of childhood trauma will, in a functional neuroimaging paradigm, show less activation in the hippocampal and ACC regions during spatial cognitive tasks.

Method

Participants

The 61 individuals who participated in Study 1 were assessed for their eligibility to continue into the fMRI stage of the research. First, they underwent an in-person clinical interview that screened for the presence of the following: a history of substance abuse; a history of any DSM Axis I psychiatric disorder or Axis II personality disorder; a history of neurological disease; and current psychoactive prescription medication. The presence of any one of these led to the individual's exclusion from further participation. The reasons these exclusion criteria were set in place include the fact that previous studies have shown that some prescription medications (e.g., selective serotonin reuptake inhibitors), excessive substance abuse, and comorbid psychiatric disorders may influence brain size and functionality (Jatzko et al., 2006; Smith, 2005;). The clinical interview led to the exclusion of 31 individuals from further participation. Nine participants met the diagnostic criteria for depression, three for dysthymia, 12 for alcohol and substance abuse, and seven for panic disorder, general anxiety disorder and social phobia.

After the in-person clinical interview, nine more individuals chose to withdraw from the study.[4] In summary, then, after this screening session, 21 participants (7 who had experienced at least one moderate to severe childhood trauma but who did not carry a diagnosis of current PTSD, and 14 healthy controls) remained eligible for the study; they therefore constituted, respectively, the Trauma group and the Control group. Demographic and clinical profiles of these participants are presented in Table 5. As the table illustrates, there were no statistically significant between-group differences in terms of age, sex ratio, general intellectual functioning, and depressive symptomatology. With regard to another important demographic variable, education, all participants in this sample were members of the UCT student population, and therefore it can be assumed that there were no statistically significant between-group differences in this regard.

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

Table 4.

Demographic and Clinical Characteristics of the Study 2 Sample (N = 21)

	Trauma (n = 7)	Control (n = 14)	t / χ^2	p	Cohen's d
Age	20.00 (1.15)	20.71 (3.73)	-0.78	0.447	-0.41
Sex (M:F)	3:4	7:7	0.21[a]	0.647	
WASI IQ[b]	107.67 (12.42)	111.31 (11.53)	-0.52	0.613	-0.41
CTQ-SF [c]					
Sexual Abuse	6.71 (2.21)	5.14 (0.54)	1.86	0.057	0.97
Physical Abuse	9.14 (3.29)	5.64 (0.84)	2.81	0.011*	1.23
Emotional Abuse	12.71 (3.90)	6.21 (1.12)	4.34	< .001***	1.78
Physical Neglect	6.43 (1.62)	5.71 (1.14)	1.13	0.122	0.61
Emotional Neglect	12.42 (3.31)	7.07 (2.55)	3.71	< .001***	1.38
BDI-II[d]	7.2 (5.58)	4.83 (5.06)	0.39	0.931	0.56

Note. In the second and third columns, means are presented with standard deviations in parentheses. All *t*-tests were 2-tailed, calculated with pooled variance estimates unless indicated otherwise. WASI-IQ = Performance IQ on the Wechsler Abbreviated Scale of Intelligence; CTQ-SF = Childhood Trauma Questionnaire – Short Form; BDI-II = Beck Depression Inventory – Second Edition.
[a]Results of chi-squared analysis. [b]Data based on 20 participants. [c]1-tailed *t*-test, calculated with separate variance estimates. [d]Data based on 18 participants.
*p < .05, **p < .01, ***p < .001

Materials: Interviews, Questionnaires, and Neuropsychological Tests

Mini International Neuropsychiatric Interview (MINI). This instrument (Sheehan et al., 1998) was used to screen for participants with any major psychiatric disorders. It was chosen because of its psychometric properties, conciseness and ease of administration. The MINI is a well-established structured diagnostic interview that assesses the major DSM Axis I psychiatric disorders, including depression, substance abuse and PTSD; and the DSM Axis II personality disorders, including antisocial and OCD disorders. The MINI has good inter-rater and test-retest reliability and good validity in relation to other structured clinical interviews (Sheehan et al. 1997), and has been used extensively in psychological research in South Africa (see, e.g., Kaminer, Stein, Mbanga, & Zungu-Dirwayi, 2001; Van der Ryst et al., 2002). It contains precise questions and a dichotomous response format, and therefore can be administered within approximately 20 minutes.

Beck Depression Inventory – Second Edition (BDI-II). The BDI-II (Beck, et al., 1996) was described in Study 1. In this study, those individuals scoring above 19 (the cut-off score between mild and moderate depression) were excluded from further participation in the

study. Previous research has indicated a strong association between traumatic exposure and depressive symptomatology (Breslau et al., 2000; Schnurr & Green, 2004; Shalev et al., 1998). The results of Study 1 also indicated that, in this sample, depression has some effect on cognitive performance; therefore, in order to ensure that the results of Study 2 reflected as cleanly as possible the influence of childhood trauma, and not co-morbid depression, individuals exhibiting any marked depressive symptoms were excluded from participation.

Wechsler Abbreviated Scale of Intelligence (WASI). The WASI (Psychological Corporation, 1999) was administered to assess the participants' level of general intellectual functioning. The WASI is a brief, individually administered, widely-used and robust measure of intelligence standardized and normed for individuals from ages 6 to 89. It consists of four subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning. The combined age-adjusted scaled scores of the Vocabulary and Similarities subtest provide a measure of Verbal IQ (VIQ), and the combined age-adjusted scaled scores of Block Design and Matrix Reasoning subtests provide a measure of Performance IQ (PIQ). The combined age-adjusted scaled scores of all four subtests provide a measure of Full Scale IQ (FSIQ). Because the focus of this study was on spatial cognition, the Verbal subtests were not administered and PIQ was used as an estimate of general intellectual functioning. The PIQ has been shown to be appropriate as a general measure of non-verbal intelligence, and has high internal consistency, and a reliability coefficient of 0.96 and a validity coefficient of 0.84 in adults (Strauss, Sherman, & Spreen, 2006). It has also been proven to be a successful measure in a South African population (Thornton et al., 2008).

Apparatus: Magnetic resonance imaging scanner

As noted above, this study employed functional magnetic resonance imaging (fMRI) to observe regional brain activity during virtual environment (VE) spatial navigation tasks. Functional MRI is a haemodynamic measure assessing neuronal activity indirectly, based on the assumption that in a region of increased neural activity there is a corresponding local increase in metabolism and blood flow. This blood oxygen dependent level (BOLD) contrast is a widely-used brain imaging technique because of its advanced spatial resolution, and better temporal resolution than, for example, positron emission tomography (PET), which has the added disadvantage of requiring the injection of radioactive contrast agents (Arthurs & Boniface, 2002).

T2*-weighted echo planar (EPI) images with BOLD contrast were acquired using the 3-Tesla Siemens Allegra MRI scanner at CUBIC (Cape Universities Brain Imaging Centre). fMRI software and stimulus presentation equipment were available on this scanner. Standard

scanning parameters were used to achieve whole brain coverage: 34 slices, 3 mm thick (1 mm gap), TR = 2 s, TE = 30ms, matrix size 64 x 64.

Apparatus: Virtual Environments

The use of VE spatial navigation tasks allows researchers to conduct empirical tests of spatial cognition theory without incurring the costs associated with the construction of real-world analogs of tasks such as the Morris Water Maze (MWM; Morris, 1984). Research in this field has demonstrated many advantages of using a VE, including: (a) After learning in a VE, humans can make accurate judgements about metrics in real space; (b) there is a good transfer of spatial information from virtual to real environments; and (c) this technology can assist in investigating individual differences in spatial abilities (Astur et al., 2002; Loomis, DaSilva, Fujita, & Fukusima, 1992; Loomis, Lippa, Klatzky, & Golledge, 2002; Thomas, 2003; Worsley et al., 2001). In short, investigating human spatial cognition and behaviour has been made easier, and often more efficient, by the development of VE tasks such as those described below. Furthermore, the data from virtual reality maze navigational tasks have contributed to our understanding of the neural pathways underlying spatial cognitive systems (Roche et al., 2005).

The VE spatial navigation tasks used in this study took two forms: a small-scale spatial navigation task, the Computer-Generated Arena (CG Arena; Jacobs, Laurance, & Thomas, 1997; Jacobs, Thomas, Laurance, & Nadel, 1998), and a large-scale spatial navigation task based on an environment created by Maguire et al. (1998).

CG Arena. This is a desktop-based, non-immersive VE spatial navigation task that was developed to be a human analogue of the MWM. It has been shown, across numerous studies, to be a reliable and valid measure of different forms of spatial navigation in humans (see, e.g., Laurance et al., 2002; Thomas, Hsu, Laurance, Nadel, & Jacobs, 2001). The CG Arena was developed in order to measure hippocampal functioning and spatial cognition in humans (Jacobs, Laurance, & Thomas, 1997; Jacobs, Thomas, Laurance, & Nadel, 1998; Thomas et al., 2007), and successful performance of CG Arena tasks is dependent upon intact hippocampal functioning (Frakey, Shrikisoon, Thomas, Jacobs, & Bauer, 2005; Hsu et al., 2000; Thomas et al., 2001).

In the CG Arena, as in the MWM and in other navigational VEs, participants use representations of distal cues, and the multiple spatial relations between them, to form a cognitive map of the virtual space. This map can then be used to relocate specific places within the environment (Maguire, Burgess, & O'Keefe, 2002; Maguire et al., 1999; Sandstrom, Kaufman, & Huettel, 1998).

With specific regard to the CG Arena, it has been used in a variety of research studies featuring diverse populations, such as traumatic brain injury patients (Skelton, Bukach, Laurance, Thomas, & Jacobs, 2000), children diagnosed with autism spectrum disorders (Daniels, 2009; Edgin & Pennington, 2005), older adults (Laurance et al., 2002; Thomas, Laurance, Luczak, & Jacobs, 1999), and anterior temporal lobectomy patients (Frakey, Shrikisoon, Thomas, Jacobs, & Bauer, 2005; Thomas, 2003; Cotton, 2009).

The CG Arena is normally run on a desktop personal computer and monitor by custom-designed software. The participant sits in front of the monitor and uses a joystick to navigate through the environment. In this study, the VE was projected onto a screen behind the bore of the MRI magnet; the participant, while lying down in the scanner, viewed the VE through mirrors that were attached to the standard head coil.

The experimental room in the CG Arena VE is a circular arena contained within a square room. On each wall of the room is a set of landmarks (distal cues) that may be varied by the researcher. Figure 2 shows four views within the experimental room. As can be seen, the background to each wall is the same striped wallpaper design, but each of the four walls displays a different picture. In the Arena used in this study, one wall showed a photograph of a bee pollinating some flowers. Across from that wall was a wall featuring a photograph of a diver under water. A third wall featured a photograph of water lilies in a lake. Across from the latter was a wall featuring a photograph of a tree in the mist.

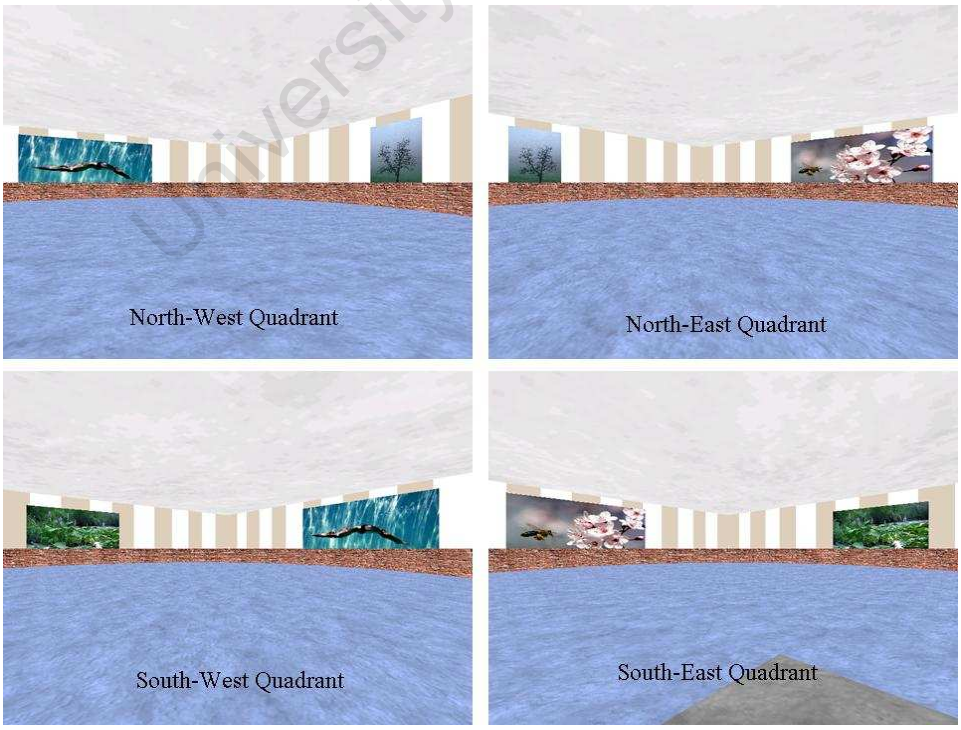

Figure 2. The experimental room in the CG Arena

Participants used an MRI compatible joystick to navigate, from a first-person perspective, through the arena. The task was to search for a square target located on the arena floor. In some conditions the target was visible and the participants had to locate it by simply scanning the floor for it (i.e., the target's location was signalled by a proximal cue). In other conditions, the target was invisible (i.e., hidden underneath the floor of the room) and the participants had to locate it by using the distal cues and the relations among them (Jacobs et al., 1997, 1998; Thomas et al., 2001). When the participants locate the target, it becomes instantly visible and they are then transported to a different starting location and, again, must search for the invisible target using the same distal cues.

Participants were also administered a companion task to the CG Arena: The *Arena Reconstitution Task* (*ART*).

The ART (Thomas et al., 2001) required the participant to reconstruct the spatial layout of the experimental room. The participant was given a stimulus sheet similar to that shown in Figure 3, as well as eight small pieces of laminated cardboard, each bearing a representation of a colour photograph from the experimental room. The participant was told that the stimulus sheet was a top-down representation of the experimental room, and was then asked to place each piece of cardboard in the appropriate space on the sheet. Finally, the participant was asked to indicate (by marking an X on the sheet) in which of the four squares the invisible target had been located.

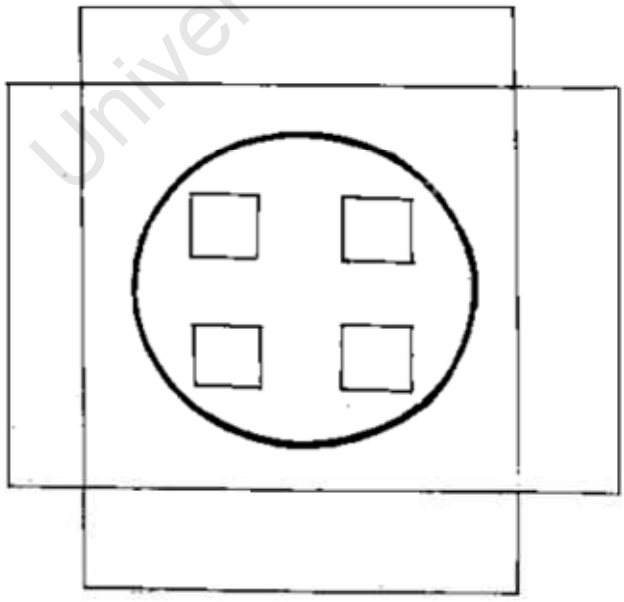

Figure 3. ART stimulus sheet

The ART is a measure of cognitive mapping ability. Previous studies have demonstrated that the ART provides data congruent with the data gathered from the CG Arena itself (Skelton et al., 2000; Thomas, 2003).

Virtual City. Following Maguire (1998), members of our laboratory created a unique VE that modelled a generic city, consisting of roads as well as a variety of landmarks and features found in most urban environments (e.g., parks and buildings, including a store, a garage, a sports stadium and a hotel). This type of VE has been used in numerous previous neuroimaging studies and has proven to be an effective measure of wayfinding (see, e.g., Maguire et al., 1999, 2000; Maguire, Frackowiak, & Frith, 1997; Spiers et al., 2008).

In the current study, the Virtual City task was set up in the scanner in exactly the same way as the CG Arena was. Participants were required to first follow a path through the city (ARROW Trial). They were required to follow dashed arrows through various parts of the city, exposing them to a variety of locations. After this trial, they were instructed to navigate freely through the city to find particular locations (Free Navigation Trial), which they navigated past in the ARROW trial. Figure 4 shows certain scenes, used in the virtual city.

Figure 4. Scenes from the Virtual City

Procedure

As noted above, the 61 participants from Study 1 completed a screening session to gauge their eligibility for participation in this fMRI study. This screening session entailed completion of the MINI, BDI-II, and WASI. Those who did not meet the inclusion criteria outlined above were excluded from further participation. Those who did meet the criteria were given an appointment for an MR scanning session.

The scanning session took place at the Cape Universities Brain Imaging Centre (CUBIC), which is located at Tygerberg Hospital. Before scanning, each participant was given practice runs in both the CG Arena and the Virtual City, with the explanation that tasks of a similar nature were to be completed in the scanner. Before beginning the practice runs, each participant received standard verbal instructions on how to move in the VE. These instructions prepared the participant for the VE display, directed him/her about how to move in the VE (e.g., "Pushing the joystick left or right will turn you in the corresponding direction, but will not move you sideways"), and what was required of them (e.g., "Move around the room until you have reached the target.").

In the case of the CG Arena practice runs, the participant viewed the VE on a desktop computer monitor and used a joystick to move around the arena in order to find a target on the floor. They were given 60 seconds to navigate to the target as many times as possible. This was repeated, but this time the target was invisible and they were instructed to move around the room until the target appeared. Participants were given 90 seconds to locate the target. If they found the target within the time limit, they were transported to a different starting location, and had to search for the target again. If the participant failed this task, the instructions were repeated and the participant was given another opportunity to repeat the task.

In the Virtual City training task, participants used a joystick to follow a path through a very simple urban environment, containing only a few buildings and some connecting roads. This task took approximately 20 seconds to complete. After this trial, they had to navigate through the simple city, for 60 seconds, in order to locate a target given at the start of the trial. If the target was located successfully the task ended. Again, if participants had any difficulties they were able to repeat the tasks.

These practice runs, as well as the detailed task instructions given to participants while they completed the runs, helped ensure that all participants were familiar with the tasks, and competent in navigating through the VEs before entering the scanner.

Furthermore, before proceeding with the study, all participants were again screened for eligibility for MRI scanning (see Appendix C for an example of an MRI screening form).

Immediately before entering the scanner, participants changed into hospital gowns to ensure that they were not carrying any metal objects or items that could be damaged by the scanner. A radiographer placed them in the scanner, and equipped the participants with earplugs (to help dull out the noise of the scanner) and MR compatible headphones (so that the experimenter could communicate with the subject). Head stabilization was achieved using a standard head coil and foam padding, and the participant was instructed to move as little as possible while the scanning procedures were undertaken.

In the MR scanner, each participant was first asked to relax for a 9-minute period during which localization and structural data (3D MPRAGE) were obtained. Participants were then administered both the CG Arena (228 volumes) and the Virtual City (202 volumes) functional scans.

CG Arena functional scans. The participant was instructed that the first task would be to find a visible target. Once he/she indicated readiness to begin the scan, the CG Arena program was started and a still image was presented to the participant for 20 seconds (*fixation trial*).

After the fixation trial, the participants entered the experimental room, and were reminded that they were to locate a visible target (a large grey square on the floor of the room) as quickly as possible. The participant, following a rudimentary scan of the environment, could easily see the visible target. The task then was simply to move to the target and to stand on it. When the participant reached the target, a computer-generated click sounded, the display would then change, and the participant would then find him/herself in a different starting location at the circumference of the arena. From that point, he/she had to find another visible target. This procedure was repeated for 60 seconds. In other words, the participant had to find as many visible targets as possible within 60 seconds.

Following two such visible target blocks, the participant was told that he/she would now attempt two similar hidden target blocks. The hidden target room was identical to the visible target room, except that the images on the wall were different. The hidden target room's walls depicted some water lilies, a sunset, a tree in the fog and a bee with some flowers. The trials within the hidden target blocks were formally identical to those within the visible target blocks, with the crucial exceptions that (1) the target was initially invisible to the participant (i.e., its colour blended with that of the surrounding arena floor), and (2) the target was always in the same place. Only when the participant moved onto the location of

this target did the target icon (the grey square) become visible and the computer-generated clicking sound, signalling a successful search. Again, the participant began each hidden target trial at a different start point on the circumference of the arena. A summary of this part of the procedure is provided by Figure 5.

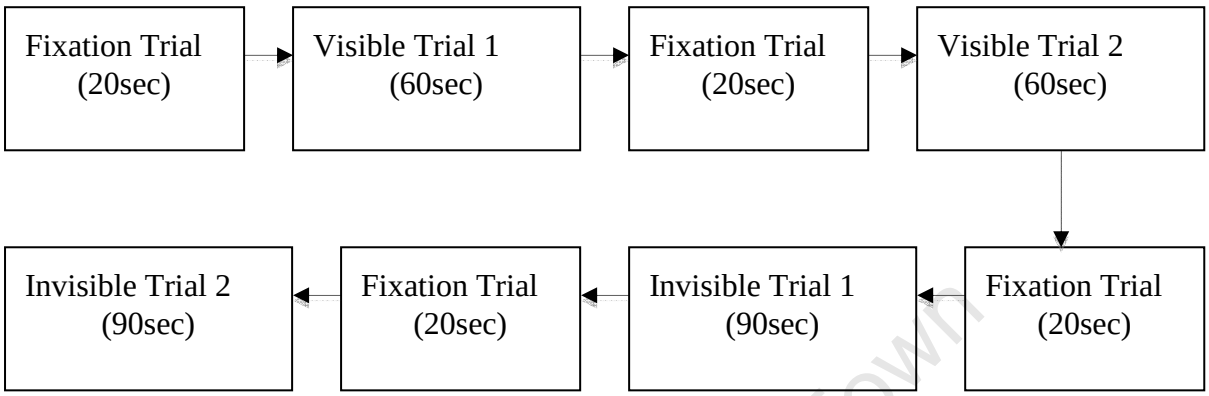

Figure 5. Procedure followed during CG Arena Tasks

Virtual City functional scans. In the virtual city, participants first viewed images of the city, to establish fixation, before each trial. During the ARROW trial, participants had to navigate around the city following arrows for a one-minute epoch. This run set a baseline for the study and allowed the subjects to become more familiar with the VE.

In the second run, participants navigated freely within the city, for a 90-second epoch, without the aid of arrows, and thus must rely on their memory from the previous runs. At the beginning of this task, a still image of a location was presented to the participant. He/she was instructed to pull the trigger on the joystick when ready; this pull allowed entrance into the city. The participant then had to navigate to the destination shown in the still image. Upon arrival at that destination, another still image was presented, displaying a picture of their next target location. Participants then had to pull the trigger and search for that location. Participants were given 90 seconds to find as many destinations as possible (Maguire et al., 1998).

Both these trials were repeated once. A summary of this part of the procedure is provided by Figure 6.

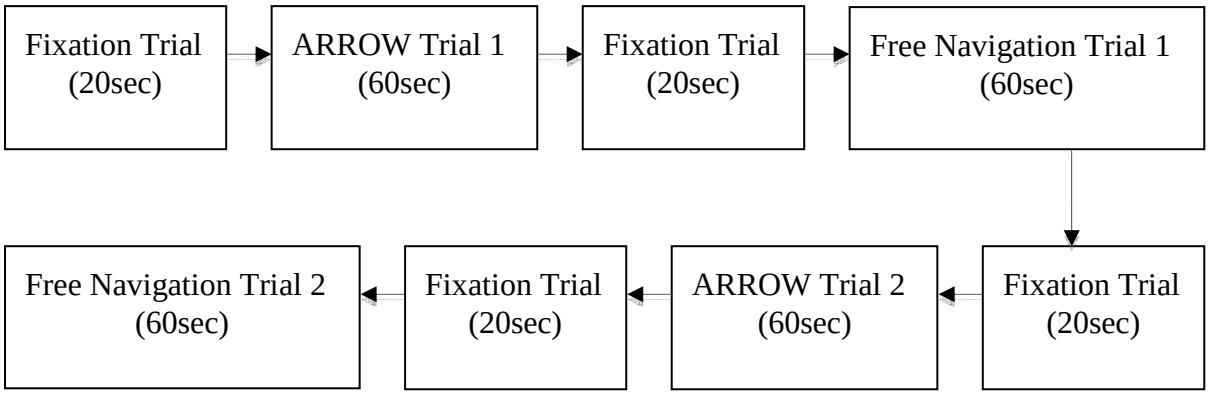

Figure 6. Procedure followed during Virtual City Tasks

The total scanning time was approximately 45 minutes per participant. After scanning protocols were completed, the participants changed back into their normal clothes and were then instructed to complete the ART. After completing this task, the participants were fully debriefed.

Statistical Analysis

WASI Performance Scores. The WASI Performance subtests were scored according to the procedure outlined in the battery's accompanying manual (Psychological Corporation, 1999). Raw scores from the block design and matrix reasoning tasks were converted into PIQ scores for each participant.

CG Arena behavioural data. The CG arena software produces a data file for each participant. The file contains data pertaining to the different aspects of the participant's performance on each of the trials. This file includes information about (a) path length – the distance of the route the participant took from starting point to the target (In order to ensure that learning was accurately being assessed, the length was calculated only after the first target was found.); (b) latency – the time the participant required to find the target; (c) targets found – the number of times the participant found the target; (d) dwell time - the amount of time the participant spent in each quadrant of the Arena; and (e) heading direction - the direction the participant was moving towards at defined periods during the trial.

Due to hardware problems, CG Arena data were not collected for two participants, and thus the final sample for this analysis was cut down to 19 (n = 6 in the Trauma group and n = 13 in the Control group).

Spatial navigation performance was assessed by calculating, for each participant, (a) the total number of visible and invisible targets found during the scanning session, and (b) the average path length to the target. The *a priori* predictions were:

1. On the visible target trials, participants in the Trauma group would perform as well as those in the Control group. The reason for this prediction is that these trials required a route-following navigational strategy, which is a non-hippocampal dependent task.
2. On the invisible target trials, participants in the Trauma group would perform more poorly than those in the Control group. Specifically, that the trauma group would find less targets, and have a longer average path length, compared to the control group. The reason for this prediction is that these trials required a wayfinding navigational strategy, which is a hippocampal-dependent task.

ART. A displacement score, for the invisible trial environments, was calculated for each participant. In order to do this, each of the pictures in the reconstruction task of the room was scored separately. This entailed counting the distance a particular picture icon was (when placed in the reconstruction) from the location where that icon should have been, in relation to the location of the target. The total score for the reconstruction was calculated by summing up these displacement scores for each of the distal cues. Therefore, higher scores indicate a poorer performance (i.e., icons were not placed in their appropriate locations) whereas a score of zero indicates perfect reconstruction (i.e., all the icons were placed in their appropriate locations) of the spatial layout of the experimental room. The scoring of this task reflects the placement of the distal cues in relation to the target. The *a priori* predictions for this task were that the trauma group would have higher displacement scores compared to the control group.

Virtual City behavioural data. The Virtual City software produces a file that contains information for all the participants. Information in this file gives the co-ordinates of each participant every second that they are in the city. In order to calculate the number of targets found during both free-navigation runs, the co-ordinates were used to calculate the path length to each target. When the path length fell below 700, it meant that a target had been found. The Euclidean Distance Metric was used to calculate this. The formula for this metric is:

$$\text{Distance} = \text{Square root } [(x_1 - x_2)^2 + (y_1 - y_2)^2 + (z_1 - z_2)^2]$$

The number of targets found by each participant, for both free-navigation tasks, was summed. The *a priori* prediction here was that participants in the Trauma group would find fewer targets than those in the Control group. The reason for this prediction is that these trials required a wayfinding navigational strategy, which is a hippocampal-dependent task.

fMRI data. All MRI data were analysed using BrainVoyager QX software package (version 1.10; Goebel, 2001). Preprocessing of the anatomical data was initiated by renaming all of the image files into DICOM files (i.e., a format that the software could analyse). Each participant's anatomical dataset was then loaded and converted into BrainVoyager's internal "VMR" data format. The data were resampled to 1mm resolution, and transformed into Talairach standard space.

Preprocessing of the functional data proceeded by loading and converting those data into BrainVoyager's internal "FMR" format. The first four volumes from each trial were discarded to allow for T1 equilibrium effects.

Slice-scan time correction was performed using sinc interpolation based on the information about the TR (2000ms) and the order of slice scanning (ascending, interleaved). 3D head motion correction was used to detect and correct for any head movements by spatial alignment of all volumes of a participant to the first volume by rigid body transformations.

Estimated translation and rotation parameters were inspected and never exceeded 4mm translation and 4 degrees rotation. This parameter was relaxed to compensate for the abnormal amount of movement that results from participants moving more than usual in a spatial navigation VE task. Spatial smoothing was also applied for the volume-based analysis.

In order to transform the functional data into Talairach space, the functional time series data of each participant was first co-registered with the subject's 3-D anatomical data set. After co-registration, intensity alignment was conducted. With regards to the functional-anatomical alignment, some manual adjustment was necessary to reduce, as much as possible, the geometrical distortions of the echo-planar images. A normalised 4-D volume time course (VTC) file was thus created for each participant.

With regard to the actual data analysis, a BrainVoyager protocol file (PRT) was derived for every participant's block and event-related data for both the CG Arena and the Virtual City. This represented the onset and duration of the events for the different conditions. In order to account for haemodynamic delay and dispersion, each of the predictors were derived by convolution of an appropriate boxcar waveform with a double-gamma haemodynamic response function.

A General Linear Model (GLM) multiple-subject design was used in the between-groups analysis. The GLM sets up a model (i.e., a general pattern that is expected to be seen in the data) and fits it to the actual data collected from the fMRI scans. Motion correction parameters were *z*-transformed and added as covariates of no interest to reduce noise from the scanner. Beta maps were created of the contrasts of interest for each subject and analysed at the second level using a random-effects ANCOVA in order to investigate group differences.

With regard to the CG Arena functional data, the *a priori* predictions were that there would be (a) no between-group differences in neural activation during the visible trials (performance of which is not dependent on hippocampal and PFC functioning), and (b) statistically significant between-group differences in neural activation during the invisible trials (performance of which is dependent on hippocampal and PFC functioning).

With regard to the Virtual City functional data, the *a priori* predictions were that there would be (a) no between-group differences in neural activation during the ARROW trials (performance of which is not dependent on hippocampal and PFC functioning), and (b) statistically significant between-group differences in neural activation during the free navigation trials (performance of which is dependent on hippocampal and PFC functioning).

Results

Behavioural Data from the CG Arena

Results for the CG Arena behavioural data between-group analyses are presented in Table 6. The assumption of homogeneity of variance was upheld for each comparison (i.e., Levene's test was not statistically significant in each case). Furthermore, the research design meant that the groups were unrelated and subjects were independently and randomly sampled from the population of interest. Furthermore, normal probability plots indicated that the data were normally distributed (See Appendix B).

Visible Target Trials. A one-way ANOVA was conducted using the number of targets found during the in-scanner visible target trials as the outcome variable. As Table 6 indicates, there were no statistically significant between-group differences, with accompanying small effect sizes. This piece of data confirms the *a priori* prediction that participants in the two groups would not perform differently on the visible target trials given that these trials required a route-following navigational strategy, which is a non-hippocampal dependent task.

Invisible Target Trials. Again, a one-way ANOVA was conducted using the number of targets found during the in-scanner invisible target trials as the outcome variable. As Table 6 indicates, there were no statistically significant between-group differences, with accompanying small effect sizes.

A second analysis of data from the invisible target blocks/trials/runs involved a one-way ANOVA using average path length after finding the first target as the outcome variable. Again, as Table 6 indicates, there were no statistically significant between-group differences, with accompanying effect sizes that almost approached the medium range (it should also be noted that participants in the Control group did have a shorter average path length than those in the Trauma group). This suggests that if larger groups were used more statistically significant results may have been found.

However, as a whole, these data do not confirm the *a priori* prediction that Trauma group would perform more poorly on these hippocampal dependent tasks, compared to the Control group.

ART performance. A one-way ANOVA was conducted using the ART displacement scores as the outcome variable. As Table X indicates, there were no statistically significant between-group differences, however fairly strong effect sizes were evident.

This piece of data therefore does not confirm the *a priori* prediction that participants in the Trauma group would have significantly higher displacement scores compared to the Control group. As with the between-groups comparison of average path length on the invisible target trials, the effect sizes here approach the medium range, which also suggests that if the groups were larger in size more statistically significant differences would be evident.

Table 5.

Between-Group Comparisons of In-Scanner CG Arena Performance

	Group					
	Trauma (n = 6)	Control (n = 13)	F	p	Levene's p	Cohen's d
Visible target trials						
No. targets found	11.33 (1.75)	11.38 (1.98)	0.003	0.957	0.656	-0.03
Invisible target trials						
No. targets found	13.50 (4.68)	13.85 (5.58)	0.017	0.897	0.487	-0.07
Average path length [a]	140.86 (84.78)	115.35 (87.88)	0.353	0.560	0.818	0.24
ART displacement score[b]	3.00 (0.71)	2.50 (1.27)	0.657	0.43	0.124	0.49

Note. In the second and third columns, means are presented with standard deviations in parentheses.
[a]Average path length on all invisible target trials after trial 1.
[b]Trauma group n = 5; Control group n = 10.
*p < .05, **p < .01, ***p < .001

Behavioural Data from the Virtual City

As can be seen in Table 7, there were no statistically significant between-group differences in terms of the number of total targets found in the Virtual City task, however the effect size was approaching the medium range, suggesting that larger groups may have yielded more significant results. One reason to look at the two free navigation trials separately was that we hypothesised that perhaps the second one would be more informative, given that the participants would have had three trials previously (i.e., the entire first free navigation run) in order to be fully accustomed to the VE and to the requirements of the task. The data, however, showed that there were no statistically significant between-group differences at any stage of this task. Our *a priori* predictions, that the Trauma group would find less targets in this hippocampal-dependent task, were therefore, not confirmed by the outcomes of the task.

Table 6. *Between-Group Comparisons of In-Scanner Virtual City Performance: Targets Found*

	Group					
	Trauma (n = 6)	Control (n =11)	F	p	Levene's p	Cohen's d
Free navigation						
First run	1.67 (0.82)	1.64 (1.03)	0.004	0.951	0.35	-0.03
Second run	2.17 (1.47)	2.18 (0.75)	0.001	0.978	0.06	-0.07
Total	3.83 (1.94)	3.82 (1.47)	< .001	0.986	0.37	0.24

Note. In the second and third columns, means are presented with standard deviations in parentheses.

fMRI Data Analyses

CG Arena Visible Trials. A random-effects ANCOVA was performed on the fMRI data from these trials to establish whether there were any statistically significant between-group differences in activation on this non-hippocampal dependent task. The a priori prediction here, then, was that there would be no significant between-group differences. At a corrected p threshold (using a false discovery rate (FDR)) of 0.005, however, 15 regions showed significant activation differences. Interestingly, participants in the Trauma group showed significantly more activation in 13 of these regions (including the cingulate cortex, pre/postcentral gyri and the parahippocampal gyri; see Tables 8 and 9), with lower activation in the right inferior parietal gyrus and the left middle temporal gyrus (see Table 10).

Table 7.

Regional Activation in the Right Cerebrum during CG Arena Visible Target Trials (Trauma > Control)

	x	*y*	*z*	Number of Voxels	*Max t*	*p*
Anterior Cingulate (FL)	14 (5.3)	36 (4.2)	3.1 (2.9)	521	5.07	0.00008
	11 (3.7)	-16 (5.7)	48 (1.6)	614	6.14	0.000008
	13 (1.6)	5.8 (1.3)	42 (1.8)	120	4.57	0.00024
Cingulate Gyrus (FL)	4.8 (2.8)	3 (2.6)	51 (2.9)	680	5.15	0.000067
	4.8 (1.7)	3 (1.7)	39 (1.4)	148	4.54	0.000253
	54 (1.9)	-5.1 (1.3)	25 (1.2)	121	4.74	0.000164
Postcentral Gyrus (PL)	37 (5.8)	-18 (4.8)	30 (2.5)	1149	5.80	0.000017
	30 (2.4)	-12 (1.5)	39 (2)	195	3.96	0.000909
	25 (1.6)	-20 (1.4)	58 (1.5)	115	4.80	0.000146
Precentral Gyrus (FL)	31 (3.5)	-23 (3.5)	48 (3.9)	317	4.68	0.000186
Inferior Frontal Gyrus (FL)	44 (1.3)	23 (2)	7.8 (1.8)	114	4.33	0.000408
Insula	45 (4.0)	3.9 (3.1)	5.5 (4.3)	468	4.83	0.000135
Caudate Nucleus (Tail)	24 (1.7)	-31 (4.1)	19 (4.9)	562	6.30	0.000006
Putamen	28 (2.9)	-17 (2.3)	3.4 (3.6)	324	6.36	0.000005
	23 (1.7)	12 (2.5)	27 (2.5)	339	6.36	0.000005
Corpus Callosum (FL)	19 (1.8)	1.5 (2.3)	28 (3.3)	239	5.19	0.000062
	38 (1.6)	-22 (4.2)	-15 (1.8)	200	4.26	0.000467
Parahippocampal Gyrus (LL)	26 (2.2)	-4.8 (1.3)	-12 (1.9)	137	4.90	0.000116
Lateral posterior thalamic nucleus	20 (1.5)	-19 (3)	9.7 (2.6)	258	5.14	0.000069
	50 (1.5)	-0.1 (1.6)	-15 (1.8)	132	5.25	0.000054
Middle Temporal Gyrus (TL)	48 (2.4)	-25 (1.6)	-2.7 (1.2)	178	6.30	0.000006
Superior Temporal Gyrus (PL)	56 (3.8)	-26 (2)	16 (2.7)	436	4.92	0.000111
	48 (5.3)	-11 (4.1)	7.4 (2.1)	827	5.81	0.000017

Note. Threshold; $p < 0.005$. The mean talairach coordinates are presented with standard deviations in parenthesis. FL = Frontal Lobe; LL = Limbic Lobe; PL = Parietal Lobe; TL = Temporal Lobe.

Table 8.
Regional Activation in the Left Cerebrum during Visible Target Trials (Trauma > Control)

	x	*y*	*z*	Number of voxels	*Max t*	*p*
	-10 (1.4)	-5.2 (1.8)	43 (1.4)	130	4.60	0.000221
Cingulate gyrus (FL)	-20 (1.4)	-40 (1.7)	36 (2.1)	179	5.26	0.000053
Amygdala	-26 (2.1)	-8.8 (2)	-19 (2)	163	6.17	0.000008

Note. Threshold: $p < 0.005$. The mean talairach coordinates are presented with standard deviations in parenthesis. FL = Frontal Lobe.

Table 9.
Regional Activation during Visible Target Trials (Trauma < Control)

	x	*y*	*z*	Number of Voxels	*Max t*	*p*
Inferior parietal gyrus (RC; PL)	36 (1.7)	-60 (1.9)	46 (1.9)	129	-3.96	0.000914
Middle temporal gyrus (LC; TL)	-60 (1.8)	-13 (2.4)	-12 (2.3)	177	-4.40	0.000349

Note. Threshold; $p < 0.005$. The mean talairach coordinates are presented with standard deviations in parenthesis. PL = Parietal Lobe; TL = Temporal Lobe; RC = Right Cerebrum; LC = Left Cerebrum.

CG Arena Invisible Trials. A random-effects ANCOVA was performed on the fMRI data from these trials to establish whether there were any statistically significant between-group differences in activation on this hippocampal dependent task. The *a priori* prediction here, then, was that there would be marked between-group differences.

At a corrected *p* threshold (using a FDR) of 0.005 there were no significant between-group differences. However, at a *p* threshold of 0.01, participants in the Trauma group displayed significantly less activation in five brain regions in the right cerebrum (including the ACC, the Precentral gyrus, the middle frontal gyrus (MFG), and the putamen; see Table 11). Although no activation differences were evident in the hippocampus or hippocampal formation, our *a priori* predictions were partially confirmed: Participants in the Trauma group showed less activation in the PFC, including the ACC, compared to those in the Control group.

Virtual City ARROW trials. Similarly to the CG Arena data, a random-effects ANCOVA was performed on the fMRI data from these trials to establish whether there were any statistically significant between-group differences in activation on this non-hippocampal dependent task. The a priori prediction here, then, was that there would be no real between-group differences.

However, at a corrected *p* threshold (using a FDR) of 0.005, 15 regions showed significant activation differences. These regions included the MFG, the Precuneus and the cerebellum in the right hemisphere, and the Cingulate gyrus, the MFG, the Parahippocampal gyrus and subcortical structures (namely the caudate nucleus and the putamen) in the left hemisphere. Table 13 and 14 show the regions of interest where the trauma group showed more activation compared to their healthy controls.

Virtual City Free Navigation trials. A random-effects ANCOVA was performed on the fMRI data from these trials to establish whether there were any statistically significant between-group differences in activation on this hippocampal dependent task. The *a priori* prediction here, then, was that there would be marked between-group differences.

At a corrected *p* threshold (using a FDR) of 0.005 there were no significant between-group differences. However, at a *p* threshold of 0.01, participants in the Trauma group displayed significantly less activation in two brain regions (the caudate nucleus and the superior temporal gyrus; see Table 15). Although no activation differences were evident in the hippocampus or the PFC, the fact that were marked differences in activation partially confirm our *a priori* predictions.

Table 10.
Regional Activation during Invisible Trials (Trauma < Control)

	x	*y*	*z*	Number of Voxels	*Max t*	*p*
Superior Temporal Gyrus (RC; TL)	48 (2.1)	-25 (1.5)	-3.3 (1.2)	150	-4.47	0.000293
Precentral Gyrus (RC; FL)	35 (3)	-19 (3.9)	31 (2.4)	408	-3.83	0.001238
Putamen (RC)	26 (2.2)	-15 (1.7)	7.2 (3.2)	137	-4.59	0.000229
Middle Frontal Gyrus (RC; FL)	18 (3)	58 (1.7)	11 (1.2)	125	-3.51	0.002489
Anterior Cingulate (RC; LL)	2.9 (1.4)	43 (3.2)	7.3 (1.2)	151	-4.21	0.000523

Note. Threshold; $p < 0.005$. The mean talairach coordinates are presented with standard deviations in parenthesis. FL = Frontal Lobe; LL = Limbic Lobe; PL = Parietal Lobe; TL = Temporal Lobe; RC = Right Cerebrum.

Table 11.

Regional Activation in the Right Cerebrum during ARROW Trials (Trauma > Control)

	x	*y*	*z*	Number of Voxels	*Max t*	*p*
Middle Frontal Gyrus (FL)	34 (1.6)	33 (2.6)	5.1 (6)	258	4.83	0.000186
Middle Occipital Gyrus (OL)	32 (1.7)	-80 (2.5)	18 (2.5)	153	4.45	0.000405
Superior Parietal Gyrus (PL)	22 (1.8)	-47 (2.1)	53 (2.9)	228	4.71	0.000237
	24 (1.9)	-70 (2.5)	29 (2.6)	333	4.95	0.000144
Precuneus	17 (1.3)	-58 (2)	40 (1.6)	158	4.24	0.000618
	6.7 (2.9)	-68 (2.8)	-17 (2.1)	443	5.46	0.000053
	2.1 (1.9)	-80 (1.8)	-12 (2.3)	219	4.71	0.000234
	3.6 (1.1)	-52 (2.5)	5.9 (1.4)	116	5.15	0.000097
Right Cerebellum	27 (5)	-53 (3.5)	-17 (3.4)	638	6.28	0.000011

Note. Threshold; $p < 0.005$. The mean talairach coordinates are presented with standard deviations in parenthesis. FL = Frontal Lobe; PL = Parietal Lobe; OL = Occipital Lobe.

Table 12.

Regional Activation in the Left Cerebrum during ARROW Trials (Trauma > Control)

	x	*y*	*z*	Number of Voxels	*Max t*	*p*
	-2.8 (2.7)	-1.3 (3.4)	38 (2.4)	417	5.87	0.000024
Cingulate Gyrus	-1.4 (2.1)	-22 (1.1)	50 (2.8)	116	4.23	0.000632
	-25 (4.2)	31 (2.2)	27 (1.8)	188	4.18	0.000712
Middle Frontal Gyrus (FL)	-26 (1.5)	-12 (1.7)	47 (1.7)	171	4.46	0.000395
Parahippocampal Gyrus (LL)	-14 (1.4)	-44 (3.5)	-2.5 (2)	158	4.36	0.000489
Caudate Nucleus	-16 (1.4)	-28 (2.5)	13 (1.7)	208	4.98	0.000135
Precuneus	-14 (2)	-71 (2.6)	33 (2)	287	4.71	0.000238
Superior Temporal Gyrus (TL)	-51 (2.2)	-29 (2)	14 (1.4)	230	5.95	0.00002
Inferior Temporal Gyrus (TL)	-50 (1.7)	-53 (2.2)	-12 (1.4)	121	5.35	0.000065
Lingual Gyrus (OL)	3.3 (1.6)	-72 (1.6)	-3.6 (1.5)	119	4.49	0.000373
Fusiform Gyrus (OL)	-26 (1.5)	-55 (2.1)	-5.9 (1.6)	121	4.49	0.000374
Left Cerebellum	-26 (2)	-54 (1.6)	-23 (3.1)	209	6.79	0.000004

Note. Threshold; $p < 0.005$. The mean talairach coordinates are presented with standard deviations in parenthesis. FL = Frontal Lobe; LL = Limbic Lobe; TL = Temporal Lobe; OL = Occipital Lobe.

Table 13.

Regional Activation during Free Navigation Trials (Trauma < Control)

	x	*y*	*z*	Number of Voxels	*Max t*	*p*
Caudate Nucleus (RC)	20 (2.7)	23 (1.8)	9.8 (1.7)	200	-3.57	0.002548
Superior Temporal Gyrus (TL; LC)	-56 (1.3)	-58 (2.5)	5.9 (3.9)	187	-4.20	0.000684

Note. Threshold; $p < 0.01$. The mean talairach coordinates are presented with standard deviations in parenthesis. TL = Temporal Lobe; RC = Right Cerebrum; LC = Left Cerebrum.

Discussion

In this section, the behavioural and fMRI results from both spatial navigation tasks will be discussed in detail. The discussion will deal with each subtest of each environment separately; the visible and invisible trials of the CG Arena will be dealt with first, and the ARROW and free-navigation trials of the Virtual City next. The behavioural results will be discussed and related to any marked between-group differences in neural activation.

CG Arena Visible Trials

As in previous CG Arena studies (e.g., Jacobs et al., 1997, 1998; Thomas et al., 2007), performance on the visible target trials was used here as a comparative baseline for performance on the invisible target trials. Successful performance on the visible target trials does not require the use of a cognitive mapping strategy (Jacobs et al., 1997), and thus performance of such a route-following task does not require engagement of the cognitive mapping neural network that centres on the right hemisphere hippocampus (Hartley et al., 2003). Therefore, the prediction for the behavioural results of the visible target trials was that there would be no between-group differences in performance; participants with possible hippocampal compromise (i.e., those in the Trauma group) would perform just as well as those with no such compromise (i.e., those in the Control group). The obtained behavioural data confirmed this hypothesis: On average, participants in the two groups found almost exactly the same number of visible targets.

Considering the fact that no behavioural between-group differences were evident on the visible target trials, I further predicted that there would be no between-group differences in activation during fMRI of navigation during visible target trials. The obtained data did not confirm this hypothesis, however: On average, participants in the Trauma group showed statistically significantly more activation in 13 regions compared to those in the Control group. One interpretation of this pattern of data is that, taking into account the behavioural results, participants in the Trauma group had to employ more brain activity to achieve the same results as those in the Control group.

Most of this increased activation was seen in the right frontal cerebrum, in particular the cingulate cortex and the precentral/postcentral gyrus. With regard to the former region, the anterior cingulate cortex (ACC), along with the dorsolateral prefrontal cortex (dlPFC)

plays an important role in cognitive control[5] and is involved in maintaining attention and monitoring responses when faced with novel stimuli. Numerous neuroimaging studies have shown that the ACC is particularly involved in monitoring internal states for any indications that adjustments need to be made in processing or performance in a task (Kerns et al. 2004; MacDonald et al., 2000). The current data therefore suggest that, during completion of the CG Arena visible target trials, participants with a history of childhood trauma had to employ more attentional and performance control to achieve the same results as those with no such history.

This interpretation of the data is consistent with PTSD studies that have linked altered ACC and dorsal-attention function as possible neural markers of attentional problems in PTSD (Bryant et al., 2005; Hayes, LaBar, Petty, McCarthy & Morey, 2008). For instance, Hayes and colleagues (2008) investigated the neural substrates underlying attention and emotion in association with PTSD symptomatology. Using the Davidson Trauma Scale (DTS; Davidson et al., 1997), a group of 23 combat veterans was divided into with a subset of those with more PTSD symptoms and a subset of those with fewer symptoms. fMRI analysis was conducted during a modified oddball paradigm, in which participants had to discriminate infrequent target stimuli (in this case circles) from frequent targets (squares) while emotional and neutral distractors were presented. The high-symptom PTSD group showed attenuated activation in dlPFC for targets during the neutral trial and greater activation in the ACC and ventral-limbic regions during the emotional trial. On the basis of these results, the authors suggested that hyperresponsive ventral-limbic activity coupled with changes in dorsal-attention and ACC function may be a neural marker of attention bias in PTSD.

Another brain region involved in cognitive control is the middle frontal gyrus (MFG), which is part of the dlPFC. Relative to control participants, individuals in the Trauma group showed increased activation in this region during completion of the visible target trials. Again, neuroimaging studies have shown that the dlPFC is involved in maintaining and adjusting behaviour according to the attentional demands of a task (MacDonald et al., 2000). The centrality of this region to attentional control has also been proposed by studies linking the MFG to performance of spatial working memory tasks (Leung, Gore & Goldman-Rakic, 2002; McCarthy et al., 1994). In the current task, each time the participant successfully located the target he/she was transported to a novel starting position at the circumference of

[5]This term refers to the neural mechanisms that can override or augment reflexive and behavioral reactions to ensure that behavior is adjusted in accordance with our intentions (Miller, 2000).

the Arena, and from there had to attend to the location of the visible target before moving towards it. It is possible that the MFG is at least partially responsible for this attentional action.

Participants in the Trauma group also showed relatively increased activation in the superior temporal gyrus (STG) during completion of the visible target trials. Neuroimaging studies of the neural networks underlying attentional function consistently show the STG, as well as the ACC, to be activated in tasks that require cognitive control (Hopfinger, Bunocore, & Mangun, 2000, Hopfinger, Woldorff, Fletcher, & Mangun, 2001). For instance, Hopfinger and colleagues (2001) used event-related fMRI techniques to distinguish neural regions involved in attentional control from those regions involved in the subsequent processing of target stimuli during a cued spatial-attention task. These results suggested that the STG forms part of the neural network involved in cognitive control.

Other regions that showed relatively increased activity in Trauma group participants during completion of the visible target trials were the precentral gyrus and the postcentral gyrus. Similarly to the ACC and MFG, these gyri have been proposed to play an important role in attentional control. In the study mentioned above, results indicated that while the ACC, MFG and STG were activated during tasks that required cognitive control, the precentral and postcentral gyri were seen to be involved in the network that modulated target processing in tasks subsequent to the engagement of this control (Hopfinger et al., 2000). Therefore, in the current study's visible target trials, increased activation in these regions (namely the ACC, MFG, STG and precentral and postcentral gyri), in participants with a history of childhood trauma, suggests that these individuals required more top-down cognitive control in order to complete the task as successfully as those in the Control group.

During completion of the visible target trials, participants with a history of childhood trauma also showed increased activation, relative to participants with no such history, in the caudate nucleus and the putamen. Previous neuroimaging studies have shown that both these regions are involved in learning (particularly motor learning). For instance, Jueptner et al. (1997) found strong activations in the caudate nucleus during new motor learning tasks. The putamen showed activations during tasks that were similar but did not provide the participants with feedback, which is used to prompt appropriate behavioural adjustments. Strong activations were also evident in both regions when subject repetitively made the same movements. Recent studies have also shown these regions to be preferentially engaged during route-following tasks (Bohbot et al., 2004; Hartley et al., 2003; Iaria et al., 2003). For instance, Hartley and colleagues (2003) investigated the neural bases of route following and

wayfinding in a virtual environment. The fMRI data of 16 right-handed males showed marked increases in activation in the caudate nucleus during route-following tasks compared to wayfinding tasks. Bohbot et al. (2004) showed similar activations in both the caudate nucleus and the putamen during a task that required a route-following strategy, in comparison to a task that required a spatial wayfinding strategy.

Finally, during completion of the visible target trials participants with a history of childhood trauma showed increased activation, relative to controls, in the parahippocampal gyrus. This brain region has been isolated as one of the critical neural substrates involved in spatial navigation (Aguirre, Detre, Alsop, & D'Esposito, 1996; Aguirre, Zarahan, D'Esposito, 1998), especially in the passive processing of scenes and when object-location associations are required (Epstein & Kanwisher, 1998; Owen, Milner, Petrides, & Evans, 1996). Further neuroimaging evidence suggests that the parahippocampal gyrus is particularly active in environments featuring salient objects and landmarks (Maguire et al., 1998). This evidence, coupled with behavioural data from previous CG Arena studies (Jacobs et al., 1997), suggests that participants in the Trauma group (but not those in the Control group) were engaging in cognitive mapping of the CG Arena VE during the visible target trials. Obviously, cognitive mapping of the environment is not necessary for successful completion of visible target trials, but the fact that Trauma group participants did so is consistent with the idea that they used a wider recruitment of brain regions, compared to the controls, in the completion of these navigation tasks.

In summary, on the visible target trials participants with a history of childhood trauma tended to show increased activation, relative to participants with no such history, in brain regions involved in attention regulation and spatial navigation. The fact that, behaviourally, participants in the Trauma group performed as well as those in the Control group suggests that the former had to recruit more neural activity merely in order to achieve the same results. It is possible that the Trauma group compensates for any neural dysfunction through a plastic reorganisation of neurocognitive networks, and therefore shows more activation during this route-following task compared to the Control group.

Cabenza, Anderson, Locantore, and McIntosh (2002) used fMRI techniques to investigate differences between older adults and younger adults in the recall and source memory of recently studied words. They found that older adults who performed more poorly than young adults recruited similar right PFC regions as young adults, whereas older adults who performed as well as young adults engaged the PFC regions bilaterally. This bilateral

activation in high-performing older adults is consistent with the idea that these individuals recruit more widely in order to counteract age-related decline (the compensation hypothesis).

Before ending this section, there has to be mention of regions in which participants in the Trauma group showed decreased activity relative to participants in the Control group during the visible target trials task. These regions were the inferior parietal gyrus (IPG) in the right hemisphere and the middle temporal gyrus (MTG) in the left hemisphere. Maguire et al. (1998) suggest that the IPG uses information provided by the hippocampus to compute the correct body turns to enable movement toward the target relative to the environment. This fact implies that either participants in the Trauma group were not able to perform this computation as effectively as those in the Control group, or that they did not need to perform this calculation in order to complete the task successfully. The current study and the obtained data cannot rule out either one of these explanations, and so this question remains a matter for future investigation.

Relatively decreased MTG activation in Trauma group participants may suggest a dysfunction in the neural network involved in spatial attention (Kim et al., 1999), in which the MTG is thought to play a role. The fact that regions in the brain form part of a larger neural network implies that problems in specific areas would affect other regions involved in the same network. It is possible that because of decreased activity in the IPG and MTG (regions involved in movement and spatial navigation), the other connected regions involved in spatial cognition, namely the ACC, MFG, and STG (regions particularly involved in cognitive control), needed to increase in function in order successfully complete the visible target trials.

CG Arena Invisible Trials

As in previous CG Arena studies (e.g., Jacobs, et al., 1997, 1998; Thomas et al., 2007), performance on the invisible target trials was used here as the primary outcome measure of cognitive mapping ability. Successful performance on the invisible target trials requires the use of a cognitive mapping strategy (Jacobs et al., 1997, 1998), and thus performance on such a wayfinding task requires engagement of a neural network that centres on the right hemisphere hippocampus (Hartley et al., 2003). Therefore, the prediction for the behavioural results of the invisible target trials was that there would be statistically significant between-group differences in performance: participants with possible hippocampal compromise (i.e., those in the Trauma group) would perform more poorly than those with no such compromise (i.e., those in the Control group).

The obtained behavioural data did not confirm this hypothesis, however: On average, participants in the two groups found almost exactly the same number of invisible targets. Participants in the Trauma group did, however, take longer (but not statistically significantly longer) path lengths to find the target than those in the Control group, suggesting they adopted less efficient search strategies. One way to account for this lack of statistically significant between-group differences is that, because the participants in the Trauma group did not have any PTSD symptoms and are healthy members of the student population, their deficits therefore should not be as pronounced as those that might be present in a PTSD sample or in a sample with clear and definite hippocampal damage. It may also be assumed that the magnitude of the effect size in the relationship between a PTSD group and healthy controls would be larger than between a non-PTSD trauma group and controls. This implies that the non-PTSD trauma and control groups are closer in performance to one another than the PTSD and controls, suggesting that larger numbers in the groups would be required to statistically detect differences between a non-PTSD trauma group and healthy controls.

Despite the fact that there were no statistically significant between-group differences in performance on the invisible target trials, the fMRI data suggested that participants in the Trauma group showed less neural activation than participants in the Control group in several regions, including the ACC, the MFG, the precentral gyrus, and the putamen.

First, with regard to the ACC and the MFG, as mentioned previously numerous studies have shown that these frontal regions are involved in cognitive control. More specifically, the ACC is involved in monitoring internal states for any signs that changes need to be made in the processing or performance of a task, whereas the MFG (as part of the dlPFC) is typically activated when behavioural adjustments are made in response to a conflict in the environment (Kerns et al. 2004; MacDonald et al., 2000).

The type of cognitive control in which the ACC and MFG are involved is critical to effective performance on CG Arena invisible target trials. In other words, participants need to be able to attend to the proximal and distal cues in the VE and to react swiftly to changes in the position from which they start to search for the target. Such cognitive control is essential if the participant is to learn where the invisible target is placed and to relocate it across multiple trials. Relatively decreased activation in the ACC and the MFG therefore suggests relatively dysfunctional attentional control; this dysfunction may account for the fact that, on average, participants in the Trauma group took relatively longer path lengths to the target.

Second, with regard to the precentral gyrus, as mentioned above this cortical region is also associated with attentional control and with target processing (Hopfinger et al., 2000).

Hence, similarly to the ACC and MFG, relatively lower activation in this region may indicate less attentional control and thus explain the fact that, on average, participants in the Trauma group took slightly longer path lengths to the invisible target.

Third, with regard to the putamen, as mentioned above this region is involved in the learning of new motor sequences (Jueptner, Frith, Brooks, Frackowaik & Passingham, 1997). Furthermore, animal studies have shown that lesions in this region cause disturbances in spatial navigation (Oliveira, Bueno, Pamarico, & Gugliano, 1997), while enhancement drugs injected to the region strengthen both place- and response-learning navigational strategies (Packard, 1999). Importantly in the context of the current findings, the putamen receives input from the MFG. This suggests that the entire network involved in attentional control is not activated as much in Trauma group participants as in Control group participants; this relative lack of activation may underlie the mild navigational inefficiency seen in the Trauma group participants.

In summary, it appears that most of the regions in which participants with a history of childhood trauma showed relatively lower activation are involved in an attentional network. Previous studies have shown that, in health adults, these regions are primarily engaged when cognitive control is required. The current findings, then, are consistent with a literature showing that the PFC, and its associated functionality, is negatively impacted by traumatic exposure. In particular, lower ACC activation in the Trauma group participants is consistent with studies that have shown decreased ACC volumes in PTSD patients.

Comparing the results from the CG Arena visible target trials to those from the invisible target trials, it is interesting that the Trauma group participants showed increased activation during the route-following task compared to the Control group participants, but showed relatively decreased activation in some of these same regions during the wayfinding tasks. One possible explanation for this pattern of data is that individuals with a history of trauma exposure compensate for compromised attentional and navigational functioning during simple spatial tasks, but fail to adjust to more complex tasks that require increased cognitive control. However, the behavioural data for the invisible trials showed no real differences between the groups in the performance on these tasks. If the Trauma group did, in fact, fail to compensate during more complex tasks, this should have been evident in their performance. Therefore the reason that that Trauma group showed lower activation, in comparison to the Control group, during these cognitive wayfinding tasks, remains a matter for further investigation.

Finally, the obtained fMRI data did not confirm the hypothesis that there would be statistically significant between-group differences in hippocampal activation. Some possible explanations here are that (a) hippocampal functioning in the Trauma group participants is relatively intact, or (b) small-scale VE tasks, such as the CG Arena, are not complex enough to elicit behavioural dysfunctions or to show marked differences in activation in an fMRI paradigm. The Virtual City used in this project is a large-scale complex environment and therefore would perhaps elicit more significant differences between the two groups.

Virtual City ARROW Trial

As in previous studies that made use of a virtual city (e.g. Maguire et al., 1998, 1999, 2000; Maguire, Frackowiak, & Frith, 1997; Spiers et al., 2008), the ARROW trials were designed to allow the participants to become accustomed to the environment and to encode the various locations in the city. Successful performance on the ARROW trials requires the use of a simple route-following strategy, and thus performance does not require engagement of the cognitive mapping neural network that centres on the right hemisphere hippocampus (Hartley et al., 2003). Therefore, I predicted that there would be no between-group differences in activation during fMRI of navigation during ARROW trials. The obtained data did not confirm this hypothesis, however: On average, participants in the Trauma group showed statistically significantly more activation in 15 regions compared to those in the Control group. One interpretation of this pattern of data is that, similarly to the results of the CG Arena visible target trials, participants in the Trauma group, because of compromised neural functioning, had to employ more brain activity to achieve the same results as those in the Control group (the compensation hypothesis).

The participants in the Trauma group showed increased activation in a number of cortical regions in the right cerebrum, including the precuneus, and the middle frontal gyrus (MFG). With regard to the precuneus, this posterior region of the medial parietal cortex has been linked to a number of higher cortical functions: (a) developing information regarding egocentric and allocentric spatial relations for body movement control, (b) retrieval of episodic memory, and (c) processing the self in relationship to an environment (Cavanna & Trimble, 2006). All of these functional neural correlates can play a role in the processing of the ARROW task. For instance, the task simulates, from a first-person perspective, the real-world experience of moving through a novel environment. Thus, the participant would need to develop both egocentric (the environment in relation to the self, and vice-versa) and

allocentric (elements of the environment in relation to one another) information about the environment

With regard to the MFG, as mentioned previously this part of the dlPFC plays an important role in representing and maintaining the attentional demands of a task (MacDonald et al., 2000). The Virtual City ARROW task requires cognitive control as participants are required to navigate through the city while at the same time being aware of their surroundings. Increased activation in this region was also found during the CG Arena visible target trials. The increased activation seen in the Trauma group, during these route following tasks, suggests that individuals with a childhood history of trauma need to engage more cognitive control, compared to healthy participants, in order to complete this task.

Individuals in the Trauma group also showed increased activation in the right cerebellum during this task. The cerebellum is a subcortical region known to be involved in co-ordination, and visuo-motor cognition (Gazzaniga et al., 2002). The nature of the task, and the fact that the scanner requires the participant to remain as still as possible, requires hand-eye coordination, as well as skilled control of movement. Again, it can be suggested that the Trauma group needed increased functionality in this region, in comparison to the Control group in order to complete the task.

During completion of the Virtual City ARROW trials, participants in the Trauma group also showed relatively increased activation in numerous regions of the left cerebrum (including the cingulate gyrus, the MFG, the STG and the parahippocampal gyrus). The corresponding regions in the right cerebral hemisphere were relatively more active in Trauma group participants during completion of CG Arena visible target trials. The functional correlates of these right hemisphere regions were discussed above; neuroimaging studies (e.g., McDonald et al., 2000) have shown that the corresponding left hemisphere regions have similar functions but have a more language aspect to them.

The Virtual City, in comparison to the CG Arena, attempts to simulate a real world environment and therefore is richer in details; containing many more features and landmarks (e.g. buildings, cars, roads and trees). Perhaps because of the complexity and real-world aspect of the environment, the participants engage in a more verbal strategy of encoding the elements in the Virtual City.

Previous studies using similar real-world VE have suggested that left hemisphere activation may be attributed to the fact that, during navigation, language is used as an efficient means of deploying a descriptive system (Burgess et al., 2000, 2002). In the Virtual City task, participants are told to remember the environment while navigating the VE, and are

(presumably) utilising language as a strategy to effectively describe and remember the environment.

In summary, similarly to the interpretation made in the CG Arena visible target trials, relatively increased activity of Trauma group participants, seen in the ARROW task, might be attributed to these individuals compensating for any neural dysfunction through a plastic reorganisation of neurocognitive networks, in order to achieve the same results as the Control group participants.

Virtual City Free Navigation Trials

As in previous studies that made use of a virtual city (e.g., Maguire et al., 1997, 1998, 1999, 2000), performance on the Virtual City free navigation trials in this study was used as a primary outcome measure of cognitive mapping ability. Successful performance on these trials requires the use of a cognitive mapping strategy (Maguire et al., 1997, 1998, 1999), and thus performance on such a wayfinding task requires engagement of a neural network that centres on the right hemisphere hippocampus (Hartley et al., 2003). Therefore, the prediction for the behavioural results of the free navigation trials was that there would be statistically significant between-group differences in performance: participants with possible hippocampal compromise (i.e., those in the Trauma group) would perform more poorly than those with no such compromise (i.e., those in the Control group). The obtained behavioural data did not confirm this hypothesis, however: On average, participants in the two groups found almost exactly the same number of targets.

It was then decided to look at the number of targets found on each of the two free navigation trials separately, hypothesising that after two ARROW trials and one free navigation trial, participants would have had more exposure to the environment compared to their first free navigation trial, and therefore would find comparatively more targets during their second free navigation trial. Based on the previously outlined notion of possible hippocampal compromise, we expected that participants in the Trauma group would find fewer targets than those in the Control group during the second free navigation trial. The behavioural data, however, did not confirm this hypothesis; again, there were no statistically significant between-group differences.

One explanation for this lack of statistically significant between-groups differences perhaps lies in the Virtual City task itself. Although it was based on the Maguire environment, it was sometimes problematic in not registering if a participant found a target, which would greatly interfere with obtaining the correct results. This would mean that

sometimes the behavioural data obtained would not completely reflect the participant's performance on this task, and therefore would affect the results in this study.

With regard to the Virtual City free navigation trials fMRI data, participants in the Trauma group showed decreased activation compared to participants in the Control group in two cortical regions: the caudate nucleus in the right hemisphere and the superior temporal gyrus in the left hemisphere.

As mentioned previously, the caudate nucleus has been implicated as playing a role in motor learning (Jueptner et al., 1997). The fact that participants in the Trauma group showed decreased activation in this region, compared to controls, perhaps suggests that these individuals had some difficulties in navigating through the environment. This explanation is perhaps slightly tenuous, as the behavioural data obtained showed no differences between the two groups in performance. This suggests that more research is needed to fully explain why participants in the Trauma group showed lower activation, compared to the controls, in this region during the wayfinding task.

The STG was another region in which participants in the Trauma group showed decreased activation, compared to the Control group during this task. As mentioned previously, neuroimaging studies of the neural networks underlying attentional function consistently show the STG, to be activated in tasks that require cognitive control (Hopfinger et al., 2000, 2001). The decreased activation in individuals with a childhood history of trauma, suggest that these participants did not utilise cognitive control as effectively as the Control group. However, the fact that there were no differences in the behavioural performances, during this task, does not confirm this explanation, and therefore again suggests that more research is necessary to fully ascertain the nature of the group differences in a complex, large-scale wayfinding task.

GENERAL DISCUSSION

The general aim of this research project was to attempt to fill a gap in the literature concerning spatial cognition in adults who had experienced adverse childhood events. Although not all the results supported our *a priori* predictions, certain interesting findings were evident.

Firstly, Study 1 showed that participants with a history of exposure to childhood trauma performed significantly more poorly than control participants on complex visual-spatial memory tasks. In this regard the study confirmed *a priori* predictions, and contributed to the literature indicating an association between childhood traumatic experiences and adult visual-spatial memory.

Although the behavioural results from Study 2 showed no statistically significant differences between the two groups, participants in the Trauma group did, on average, take relatively longer path lengths to find the invisible target in the CG Arena (i.e., they performed less efficiently on a cognitive mapping/wayfinding task). Despite this statistical non-significance, the effects sizes associated with the between-group comparison were almost in the medium range, suggesting that if the number of individuals in each group were to be increased, statistical significance may be evident. Therefore, although the *a priori* predictions were not confirmed, this evidence perhaps points to the fact that participants in the Trauma group did have more difficulty than those in the Control group on this spatial navigation task.

Taking the results of both studies together, there appears to be some association between adult visual-spatial memory and spatial cognition, on the one hand, and exposure to stressful childhood events on the other. Therefore, the current results confirm findings from previous studies that showed individuals exposed to traumatic events show impaired performance on visual-spatial memory (Bremner et al., 1995; Golier et al., 2003; Lupien et al., 1997) and visuoconstructional (Emdad & Sondergaard, 2006; Gurvits et al. 2002) tasks.

Secondly, the fact that the tasks used in Study 1 tapped hippocampal and PFC functioning added to the existing body of research that shows an association between traumatic events and possible hippocampal and PFC damage (Bremner et al., 1998, 2005; Gilbertson et al., 2002; Gurvits et al., 1996; Kitayama et al., 2006; Smith, 2005; Villarreal et al., 2002; Woodward, 2004).

Study 2 of the current research attempted to confirm these findings using an fMRI paradigm. Although the fMRI data showed no differences in hippocampal activity during wayfinding tasks, significant between-group differences were evident in PFC activity. Specifically, participants in the Trauma group showed markedly lower PFC activation, particularly in the ACC, during the CG Arena invisible trials, thus partially confirming the *a priori* predictions. Thus, these findings from Study 2 were consistent with the Study 1 data in suggesting that, to some degree, individuals with a history of exposure to childhood trauma have difficulties with complex PFC-dependent tasks. These findings are consistent with other studies that have implicated the PFC as a neural region affected by traumatic events (Bremner et al., 1999; Felmingham et al., 2009; Kitayama et al., 2006; Shin et al., 2005, 2007; Vasterling & Brewin, 2005; Williams et al., 2006).

Taken together, the data obtained from both studies suggests that a specific neural network is disrupted by exposure to traumatic childhood events. The main neural regions involved in this network seem to be the hippocampal formation and the PFC, which support visual-spatial memory functioning (as tapped by the CANTAB tasks used in Study 1) and spatial navigational functioning (as tapped by CG Arena and Virtual City tasks used in Study 2). Although the fMRI results in Study 2 showed no significant decreases in hippocampal activation, in the Trauma group, during cognitive way-finding tasks, decreased activation in the right PFC was evident. These regions have been implicated in the large neural network thought to be involved in spatial cognition (Burgess et al., 2001; Maguire et al., 1999). The results of these two studies therefore confirm that cognitive dysfunction in individuals with a history of trauma exposure are rooted in disruptions in a *network* involved in visual-spatial memory, in contrast to damage to specific isolated brain regions.

Rationale for the use of a non-PTSD Trauma group

This research project focused on a non-PTSD trauma group, rather than following the lead of many previous studies and sampling from a PTSD-diagnosed population, for two main reasons. Firstly, there have been many criticisms of the DSM diagnostic system (Kirk & Kutchins, 1992), particularly with regard to PTSD (Scott, 1990; Summerfield, 2001; Young, 1995). Briefly, there has been much debate as to whether PTSD is an actual diagnostic category or merely a set of post-traumatic symptoms (O'Donohue & Elliot, 1992). If PTSD is in fact a diagnostic category, then any studies that use only a PTSD group, compared to controls, have to assume that any differences found are solely due to the development of the disorder. For instance any cognitive impairments found in a PTSD group would reflect that

these impairments are unique to PTSD. This idea is clearly problematic, and therefore it is important to investigate people with a history of trauma, rather that those who only fit the PTSD diagnosis, in order fully investigate the effect of trauma on cognition. It would be ideal, and therefore a suggestion for further research, to include a PTSD group, a traumatised non-PTSD group, and a control group in order fully dissociate between cognitive problems caused by a traumatic event, and those caused by the development of PTSD.

Secondly the reason for having a traumatised non-PTSD group to compare with controls lies in the relative lack of PTSD diagnoses in South Africa. The South African Stress and Health Study (Williams et al., 2003) found that the number of PTSD diagnoses was relatively low in context to the high rate of trauma exposure in South Africa. It is also not clear whether the diagnostic system, classifying PTSD, is reliable in a South African context, or even if the disorder exists in the same form as in other countries. Therefore, in a South African context is more pertinent to investigate the effects of trauma exposure, in individuals experienced adverse life events rather than those with a diagnosis of PTSD.

In conclusion, what also makes these findings interesting is that the trauma group used in this study did not meet a PTSD diagnosis. Many previous studies have found deficits and damage in the neural regions of PTSD individuals (Bremner et al., 1998; Gilbertson et al., 2002; Gurvits et al., 1996; Villarreal et al., 2002). The results of this study suggest that dysfunctions are evident in individuals, without PTSD, who were exposed to childhood traumas.

Limitations and Directions for Future Research

The current research featured three primary limitations that should be addressed in future research. Firstly, this study utilized only two groups of participants: those who had experienced early childhood adversity but who were not carrying a current diagnosis of PTSD, and a healthy control group. As noted above, the addition of a PTSD group would have benefited the design and perhaps have yielded some more conclusive results. For example, participants in the Trauma group only showed deficits on complex visual-spatial memory tasks, and no real deficits on spatial navigation tasks. It would also be useful in the dissociation of dysfunctions related traumatic exposure and those related strictly to PTSD.

Secondly, the sample sizes were rather small, particularly in Study 2. Small *N*'s are often a feature of fMRI research, and our groups were slightly smaller than those used in most fMRI studies. The effect sizes of some of the results suggested that larger groups might have yielded more significant group differences. The use of larger *N*'s in future research

would therefore shed more light on the nature of cognitive impairment in traumatised individuals.

Thirdly, the Virtual City programme had some quite marked limitations. Movement during the ARROW trial was too slow and therefore the participants did not have enough time to view the entire city. This meant that often during the free navigation trial participants were trying to find targets that they perhaps had not been exposed too, and thus would navigate randomly through the environment. Another problem in the VE was that area of target acquisition was too small, and therefore sometimes although the participants had found the target, the computer programme did not register this. It would be better, in future research projects, to make adjustments that allow for a smoother running program. However all these factors affected all the participants equally and therefore did not have a great impact on the results.

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APPENDIX A

Guidelines for Interpretation of CTQ-SF Scores

Table A1.

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

APPENDIX B

Normal Probability Plots

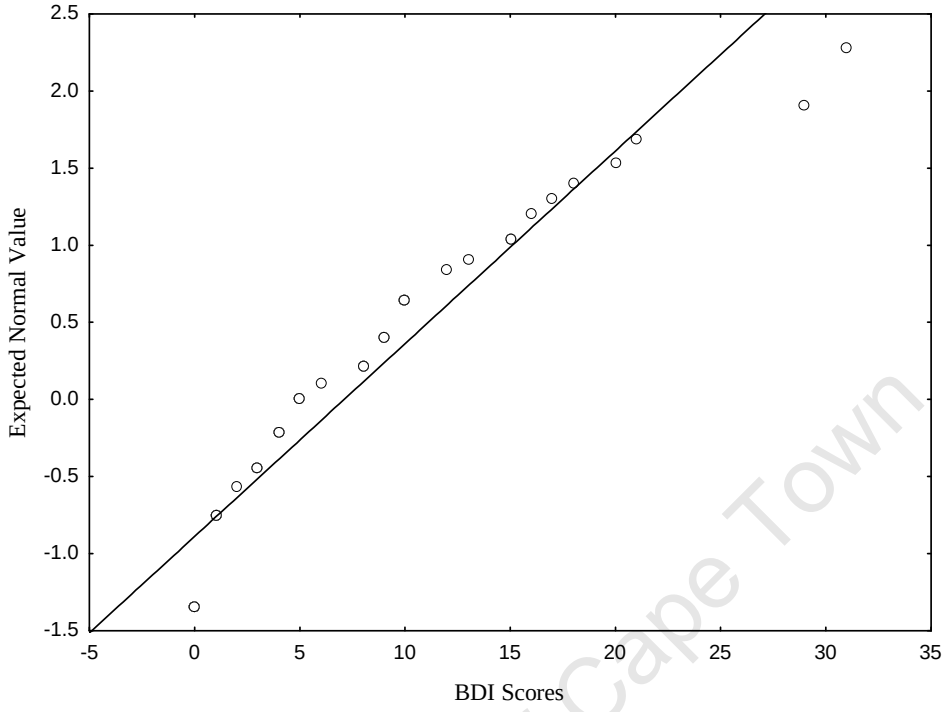

*Figure B1***.** Study 1: Normal probability plots of BDI-II scores

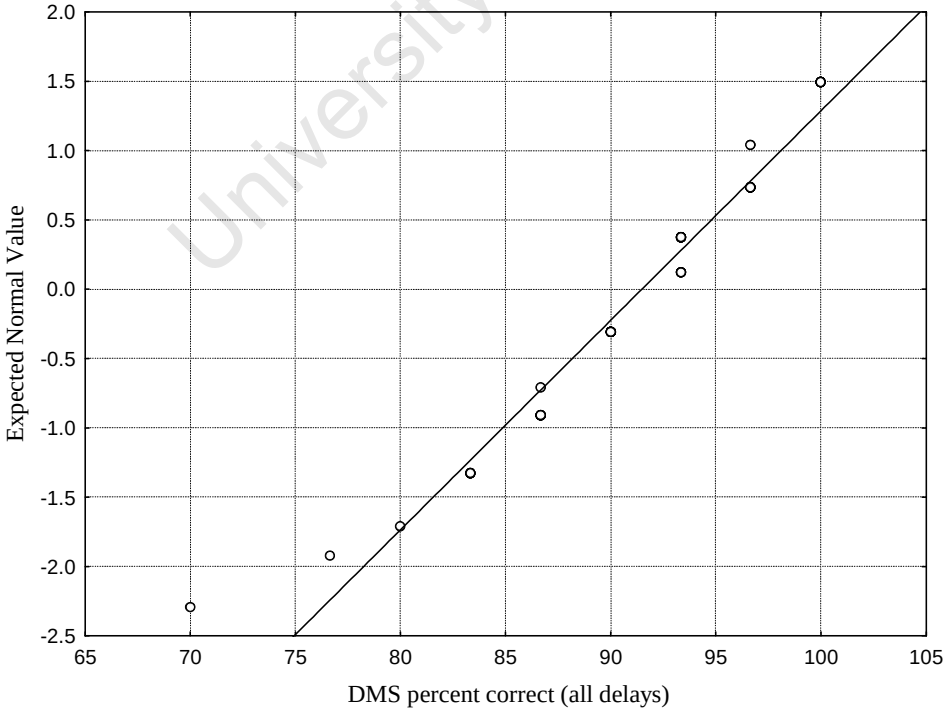

Figure B.2. Study 1: Normal probability plots of CANTAB Delayed Matching to Sample percent correct (all delays)

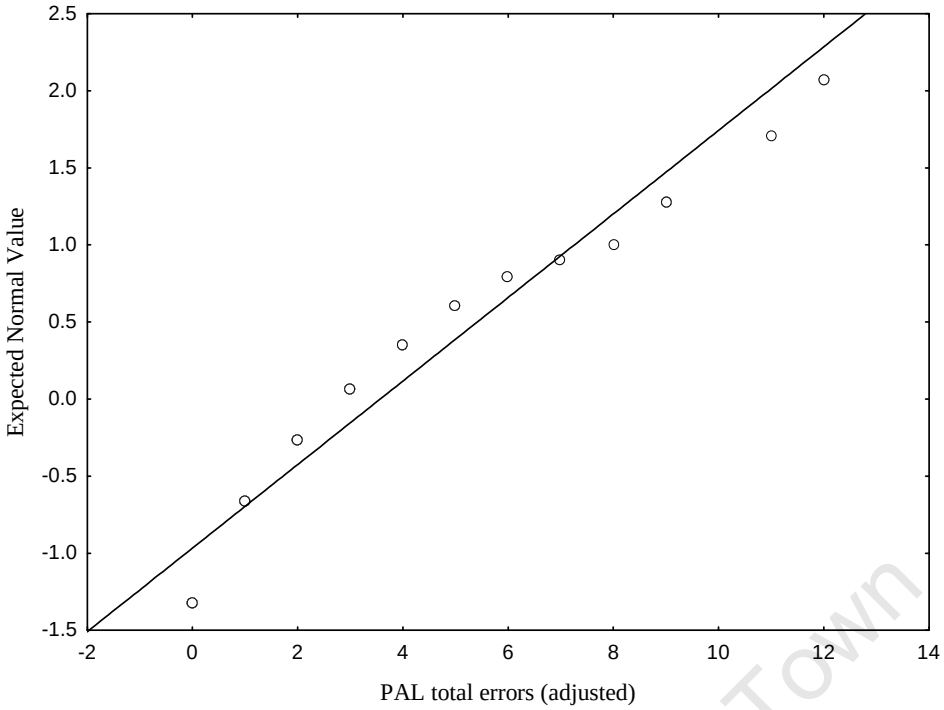

Figure B.3. Study 1: Normal probability plots of CANTAB Paired Associates Learning total errors (adjusted)

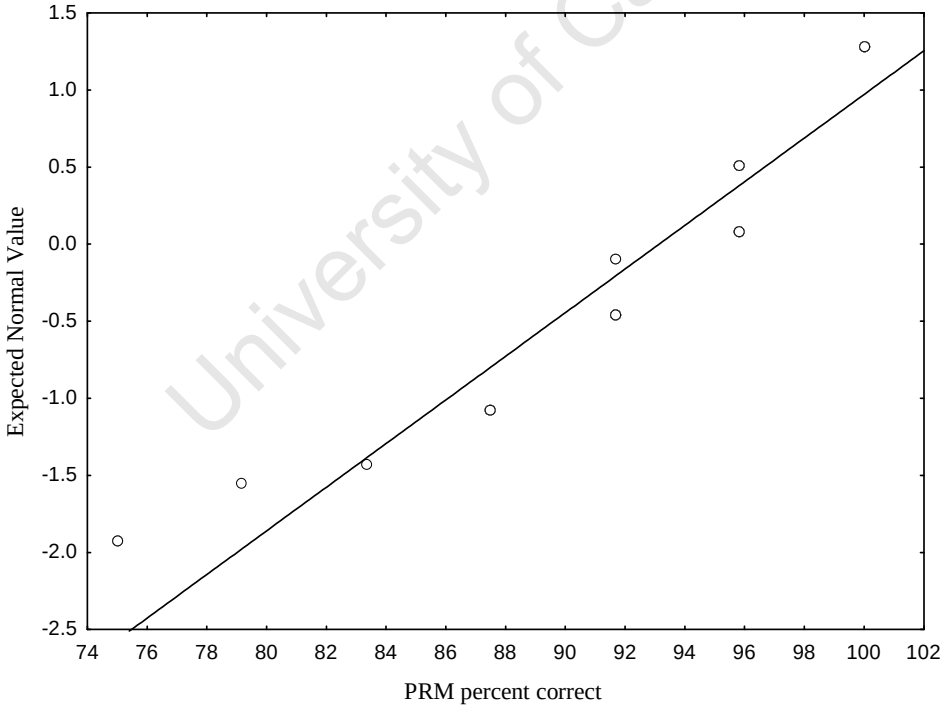

Figure B.4. Study 1: Normal probability plots of CANTAB Paired Recognition Memory percent correct

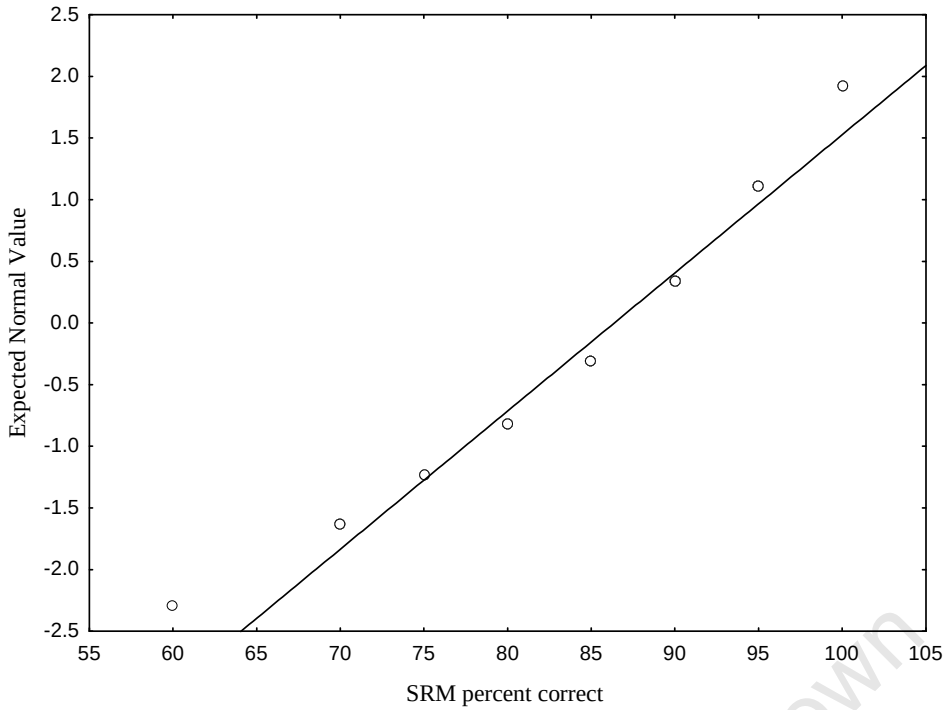

Figure B.5. Study 1: Normal probability plots of CANTAB Spatial Recognition Memory percent correct

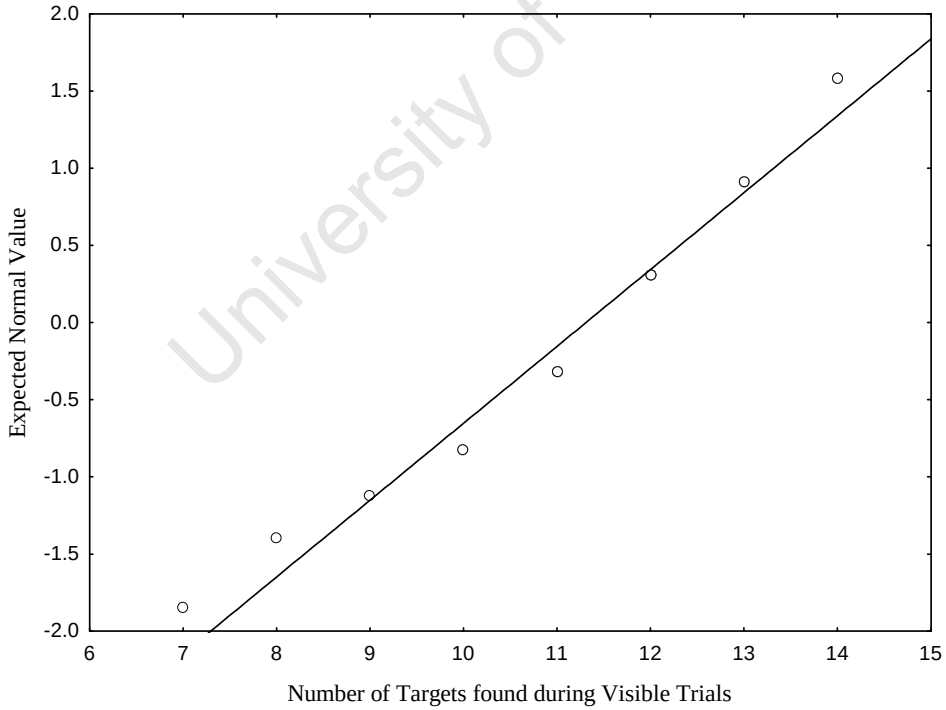

Figure B.6. Study 2: Normal probability plots of targets found during CG Arena visible trials

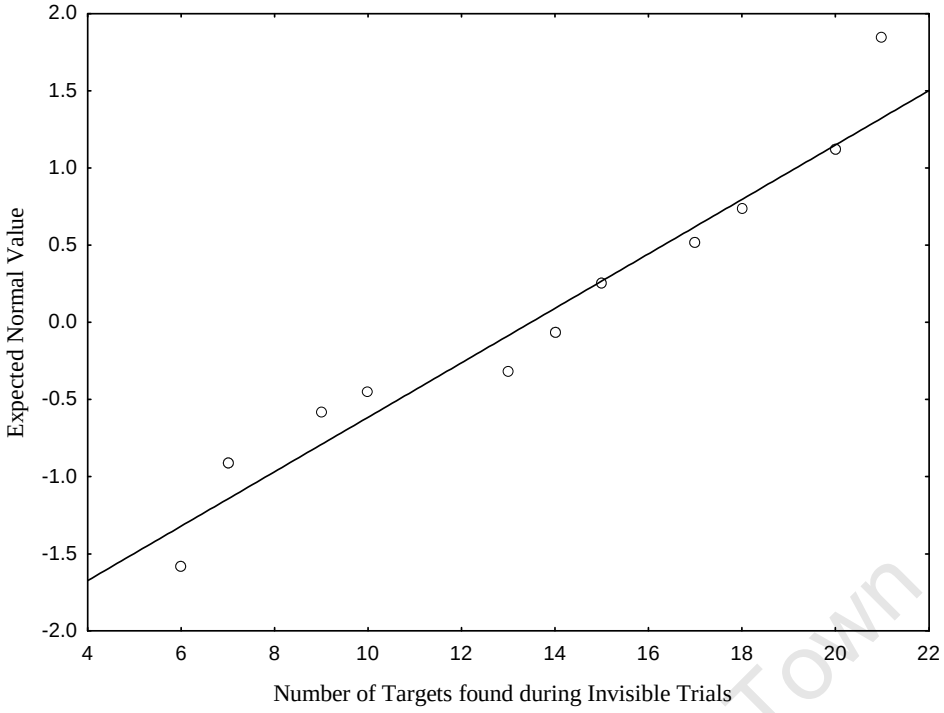

Figure B.7. Study 2: Normal probability plots of targets found during CG Arena invisible trials

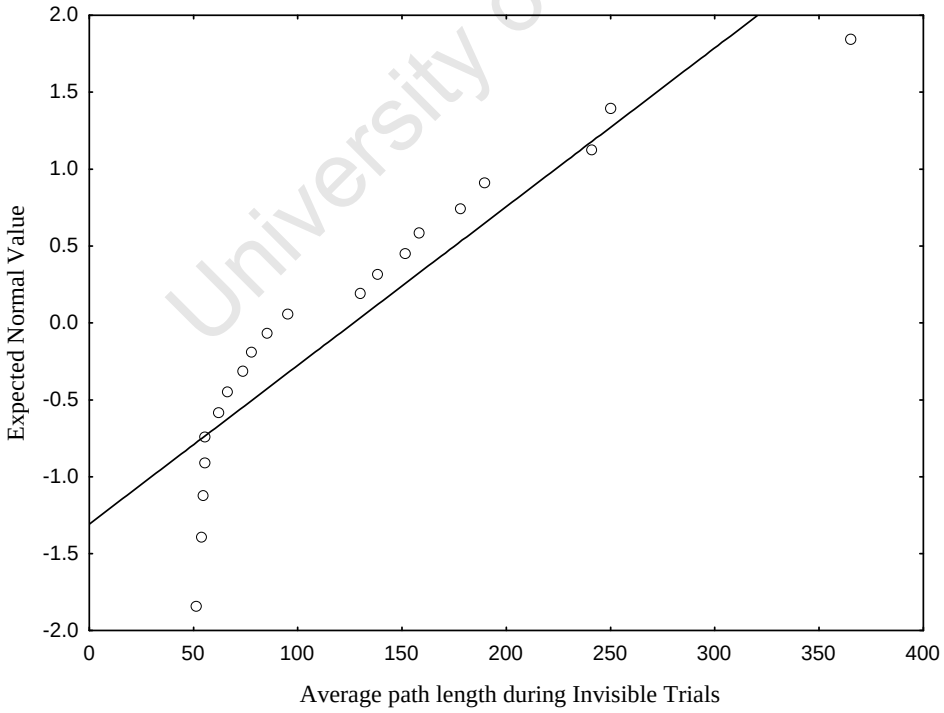

Figure B.8. Study 2: Normal probability plots of average path length during CG Arena invisible trials

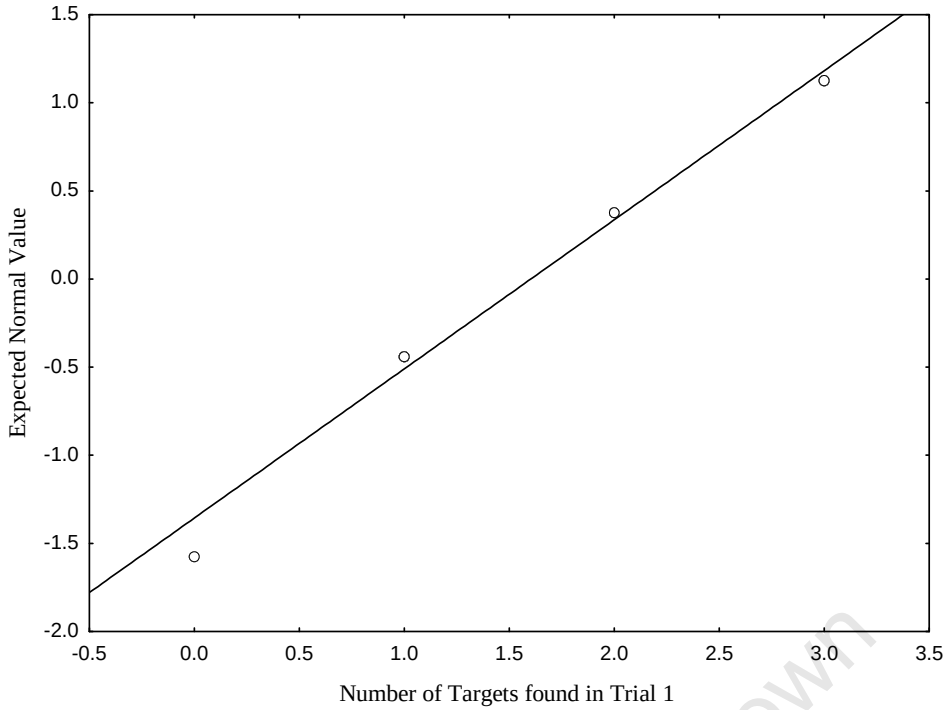

Figure B.9. Study 2: Normal probability plots of number of targets found during first free navigation trial in the Virtual City.

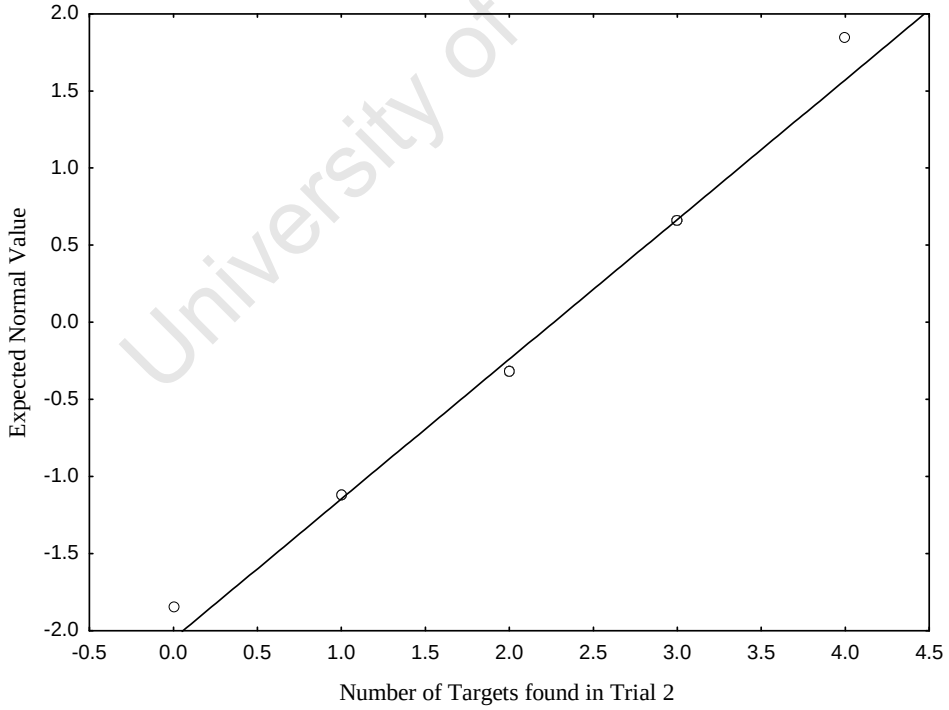

Figure B.10. Study 2: Normal probability plots of number of targets found during second free navigation trial in the Virtual City.

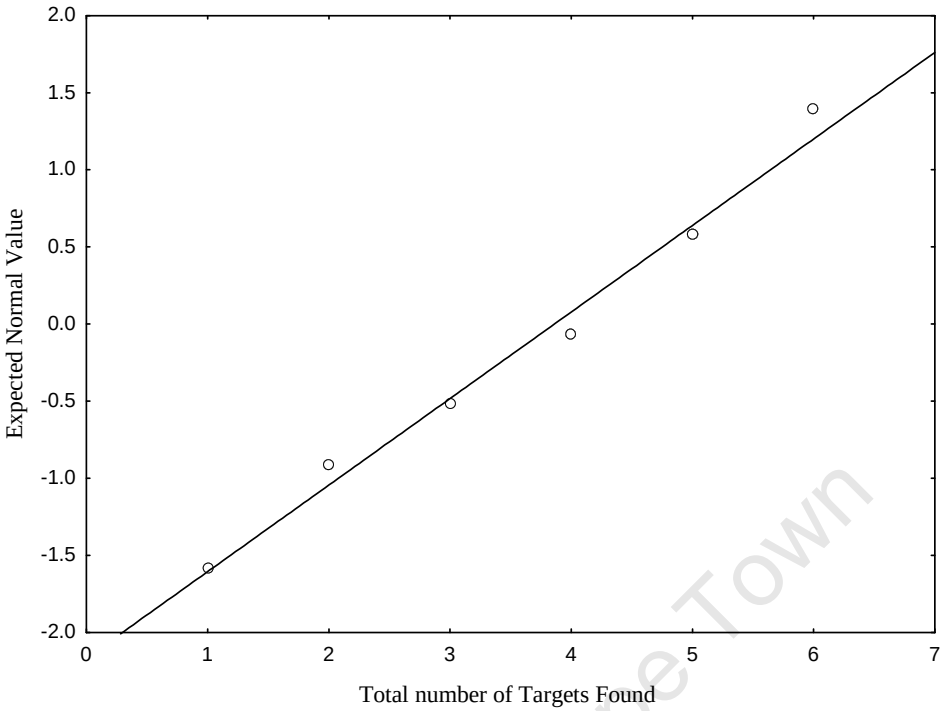

Figure B.11. Study 2: Normal probability plots of total targets found during both free navigation trials in the Virtual City.

APPENDIX C

MR hazard Checklist

THE FOLLOWING ITEMS MAY BE HARMFUL TO YOU DURING YOUR MR SCAN OR MAY INTERFERE WITH THE MR EXAMINATION.

Please mark on the drawings provided the location of any metal inside your body or site of surgical operation.

You must provide a Yes or No for every item. Please indicate if you have or have had any of the following:

YES	NO	
		Any type of electronic, mechanical, or magnetic implant. (Type:)
		Cardiac pacemaker
		Aneurysm clip(s)
		Implanted cardiac defibrillator
		Neurostimulator
		Biostimulator (Type:)
		Any type of internal electrode(s) or wire(s)
		Cochlear implant
		Hearing Aid
		Implanted drug pump (e.g., insulin, Baclofen, chemotherapy, pain medicine)
		Halo vest
		Spinal fixation device
		Spinal fusion procedure
		Any type of coil, filter, or stent (Type:)
		Any type of metal object (e.g. shrapnel, bullet, BB)
		Artificial heart valve
		Any type of ear implant
		Penile implant
		Artificial eye
		Eyelid spring
		Any type of implant held in place by a magnet (Type:)
		Any type of surgical clip or staple
		Any I.V. access port (e.g., Broviac, Port-aCath, Hickman, Picc line)
		Medication patch (e.g., nitroglycerine, nicotine)
		Shunt
		Artificial limb or joint (What and where:)
		Tissue expander (e.g., breast)
		Removable dentures, false teeth or partial plate
		Diaphragm, IUD, Pessary (Type:)
		Surgical mesh (Location:)
		Body piercing (Location:)
		Wig, hair implants
		Tattoos or tattooed eyeliner

		Radiation seeds (e.g., cancer treatment)
		Any implanted items (e.g., pins, rods, screws, nails, plates, wires)
		Any hair accessories (e.g., bobby pins, barrettes, clips)
		Jewellery
		Any other type of implanted item (Type:)

I attest that the above information is correct to the best of my knowledge. I have read and understand the entire contents of this form and I have had the opportunity to ask questions regarding the information on this form.

Patient signature: _____

MD/RN/RT signature: _____ Date: _____

Print name of MD, RN, RT: _____

_____