
PTSD and Olfaction

The Aetiology of PTSD and the Bidirectional
Relationship between Trauma and Sensitisation.

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ABSTRACT

Olfactory Identification deficits are a typical characteristic of neurological disorders and often predate their onset (e.g., Schizophrenia, Parkinson's and Alzheimer's disease). Vasterling, Brailey and Sutker (2000) investigated Vietnam veterans and found that those with Posttraumatic Stress Disorder (PTSD) had Olfactory Identification deficits. Dileo, Brewer, Hopwood, Anderson and Creamer (2008) replicated these results.

This study tested the hypothesis that olfactory deficits predict the onset of PTSD in trauma survivors. Results may inform the viability of olfactory testing as a screening tool in predicting vulnerability to PTSD.

In this prospective cohort study, patients were selected from trauma admissions to the Royal Adelaide Hospital over a 24-month period. A total of 202 injured patients were assessed during hospital admission (Time 1) and followed up at 3 months (Time 2) and 12 months (Time 3). Assessment of PTSD was with the Clinician-Administered PTSD Scale and Olfactory Functioning via the "Sniffin' Sticks" method. Tests of olfaction included Threshold, Identification and Discrimination. A binomial Generalized Estimating Equation (GEE) with logit link and logistic regression models was used to examine the relationship between Olfaction and PTSD over time.

The results contradicted the hypothesis and suggest that:

- High Olfactory Threshold at Time 1 is a predictive measure of PTSD at Time 2 and at Time 3 for females. Thus, females are more prone to PTSD if they have a high Olfactory Threshold but this relationship also existed for males at Time 2.
- High Olfactory Identification scores are significantly related to PTSD at Time 2 and Time 3. This suggests that individuals who demonstrate superior Olfactory

Identification are at increased risk of conditioning and sensitisation and following the onset of PTSD, experience a further escalation in olfactory acuity.

These results may be explained by the ‘increasing sensitisation model’ of PTSD which contends that PTSD is not an immutable, fixed condition, but dynamic and involving escalating neuropsychobiological processes (McFarlane, 2010). This escalation is mediated by neurohormonal and neuroanatomical dysfunction (van der Kolk, 1997) which influences the limbic system. Due to the extensive shared neurophysiology of the limbic and olfactory systems, much of the escalating neuropsychobiological process can be observed via olfactory functioning. Thus, olfaction becomes a window to the brain.

The dynamic relationship between olfaction and PTSD reflects this escalating nature. The likely precipitating factors behind this progression are sensitisation and kindling. Specifically a primary vulnerability marker in the development of PTSD is sensitivity to the environment. This is indicated by initial high Olfactory Threshold, which predicts PTSD. This phase in the PTSD sequence could be termed prodromal sensitisation. Following trauma those most vulnerable experience additional sensitisation until an episode of PTSD is precipitated. Once diagnosed with PTSD, kindled responses precipitate further sensitisation as demonstrated by increased Olfactory Identification and Threshold. This phase could be termed major sensitisation.

Thus, this study confirms the observation of a comorbid bidirectional relationship between trauma and sensitisation in the aetiology and development of PTSD.

The significant relationship between olfaction and PTSD means that olfactory testing has potential application in screening and prevention.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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William Graham Hough

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Olfaction is a profoundly complex, mysterious yet nuanced subject with many paradoxes. That Olfaction is related to PTSD is rather curious. Subtle is the Lord.

CHAPTER 1: INTRODUCTION

Description of the Problem

This research is concerned with the aetiology and development of PTSD. It is considered by McFarlane (2010) and others that a key component in the precipitation of PTSD is the process of escalating sensitisation. This is a particularly difficult area to examine, as it requires longitudinal research and an instrument or biological marker, which is indicative of sensitisation in relation to PTSD. The mechanisms and systems of sensitisation have not been clearly identified to date. However, change in olfactory functioning has proven to be a reliable measure which is sensitive to the progression of many neurological disorders (Doty, 1994; Barresi, Ciurleo, Giacoppo, Foti Cuzzola, Celi, Bramanti and Marino, 2012).

Olfaction has previously been measured in veterans with the chronic form of the disorder and shown to be diminished in those with long-standing PTSD (Vasterling, Brailey and Sutker, 2000; Dileo, Brewer, Hopwood, Anderson and Creamer, 2008). Nevertheless, the significance and mechanism of this finding has not been subject to adequate investigation. For instance, does olfactory dysfunction occur because of PTSD or is it a pre-existing biological vulnerability marker?

In summary, this study has observed the concomitant progression of PTSD and olfactory performance in trauma survivors to ascertain:

1. The nature of the relationship between PTSD and olfaction.
2. In addition, whether olfaction can be used as a measure of psychobiological vulnerability.

Importance of the Study

The importance of this body of work is highlighted by the fact that PTSD is one of the most prevalent of the psychiatric disorders especially amongst the veteran population. Kessler, Berglund, Delmer, Jin, Merikangas and Walters (2005) estimate that in the general

American population alone, lifetime rates for PTSD are 6.8%. Yet despite the ubiquity and the long history of PTSD, it is only in the last several decades that this disorder has undergone significant scrutiny.

A lack of research examining biological vulnerability markers, indicating sensitisation in relation to PTSD, means that further research is required. In addition, there is a limited amount of literature concerning the aetiology and development of PTSD. Part of the reason for this is that PTSD is a unique disorder in that it is not an immutable or a fixed condition, but is dynamic and involves escalating neuropsychobiological processes which change in nature and presentation over time. It is considered by authorities such as McFarlane (2010) and Shalev, Peri, Brandes, Freedman, Orr and Pitman (2000) that the mechanism driving this escalation is the effect of sensitisation and kindling. To date instruments or biological vulnerability markers indicating sensitisation in PTSD are rare, blunt (in that they are imprecise), and often do not predict vulnerability prior to trauma but immediately post trauma. For example the noted physiological response of increased heart rate following trauma predicting susceptibility to PTSD (Shalev, Sahar, Freedman, Peri, Glick, Brandes, Orr and Pitman, 1998). A study of identical twins discordant for combat exposure ascertained that increased heart rate response to sudden, loud tones was an acquired sign of PTSD, as it was not shared by the co-twins (Pitman, Gilbertson, Gurvits, May, Lasko, Metzger, Shenton, Yehuda and Orr, 2006). Although not conclusive the findings of Guthrie and Bryant (2005), Pole, Neylan, Otte, Henn-Hasse, Metzler and Marmar (2009) and Orr, Lasko, Macklin, Pineles, Chang, and Pitman (2012) suggest that sensitisation as measured by increased skin conductance response to auditory startle may possibly be used to predict the development of PTSD pre trauma.

Despite the paucity of instruments available to assess sensitisation, olfactory functioning may prove to be a valuable method to measure this construct. For instance, the neurological literature indicates that a cardinal feature of many disorders is the exhibition

of Olfactory Identification deficits. Significantly, this research demonstrates that Olfactory Identification deficits present before the neurological disorders themselves become manifest (Hawkes, 2006). This suggests that olfactory dysfunction may-be an expression of a biological vulnerability marker in these disorders.

Therefore, these findings lead to the conclusion that testing olfactory function may be a useful screening tool to determine biological vulnerability to particular neurological and psychiatric disorders. This research aimed to explore the relevance of this body of work to the investigation of PTSD. As there is no longitudinal data demonstrating the exact nature of the relationship between PTSD and olfaction further empirical research is required.

Olfactory Identification deficits have been unequivocally demonstrated in those with disorders such as schizophrenia, Parkinson's disease, Huntington's chorea, Alzheimer's and Multiple Sclerosis. Olfactory studies of those with schizophrenia have demonstrated impairments in threshold sensitivity, olfactory identification and odour recognition. However, the most salient feature about the convergence of neural pathways for schizophrenia and olfaction is that olfactory decline is one of the first symptoms of the disorder and is correlated with the progression of the disease (Fusari and Molina, 2009). Not only is this a feature of schizophrenia but also of other neurodegenerative disorders.

Despite Olfactory Identification deficits being observed in those with neurological disorders, the most important characteristic is the less recognised phenomenon of deficits being observed prior to any overt neurological symptoms. For instance this characteristic is evident in those with schizophrenia (Brewer, Wood, McGorry, Francey, Phillips, Yung, Anderson, Copolov, Singh, Velakoulis and Pantelis, 2003), Parkinson's (Ross, Petrovitch, Abbott, Tanner, Popper, Masaki, Launer and White, 2008) and Alzheimer's (Bacon, Bondi, Salmon and Murphy, 1998).

Thus, the finding that Olfactory Identification deficits predate the onset of neurological disorders has significant ramifications. For instance those who have a family history of Alzheimer's, schizophrenia or Parkinson's and have a lower than expected Olfactory Identification score may be particularly vulnerable to that disorder (Hawkes, 2006). A longitudinal study examining the relationship between olfaction and individuals deemed at high risk for psychosis found that those with Olfactory Identification deficits were more likely to develop schizophrenia later (Brewer, Wood, McGorry, Francey, Phillips, Yung, Anderson, Copolov, Singh, Velakoulis and Pantelis, 2003). This result and subsequent studies have concluded that olfactory deficits are currently one of the most predictive biomarkers of psychosis (Turetsky, Kamath, Calkins, Brewer, Wood, Pantelis, Seidman, Malaspina, Good, Kopala and Moberg, 2012).

Prior to the current investigation, three studies had been conducted examining PTSD and olfaction. Two studies tested Vietnam veterans and both found Olfactory Identification deficits in veterans with PTSD in contrast to veterans without PTSD. The authors in both studies concluded that this was due to an element of the underlying pathophysiology of PTSD, possibly orbitofrontal cortex (OFC) dysfunction (Dileo, Brewer, Hopwood, Anderson and Creamer, 2008; Vasterling, Brailey and Sutker, 2000). In contrast, the other exploratory study by Croy, Schellong, Joraschky and Hummel (2010) found enhanced odour identification in those with PTSD and no difference in threshold levels. They postulated that as odour identification reflects central processing then enhanced orbitofrontal functioning may-be the reason for this result. These contrasting results indicate further research is required to clarify the relationship between PTSD and olfaction.

Until now, no studies have been conducted to determine olfactory functioning prior to the onset of PTSD. It was hypothesised that olfactory deficits would predate the onset of PTSD based on the following:

1. the outcome of longitudinal studies, which have established the phenomena of olfactory deficits predating the onset of neurological disorders,
2. the results of Vasterling, Brailey and Sutker (2000) linking olfactory deficits with PTSD
3. the results of Dileo, Brewer, Hopwood, Anderson and Creamer (2008) further confirming this relationship.

Given that there is such a considerable overlap of the olfactory and limbic systems, one may hypothesise that dysfunction in one system would be manifest in the other. Thus, an individual with a compromised or vulnerable limbic system may present with concomitant olfactory deficits.

Thus, this study may assist in determining whether olfactory dysfunction is a predictive vulnerability marker of PTSD or a feature of PTSD. If it is the former, it has the potential to inform PTSD prevention and treatment. Ascertaining reliable markers, which identify individuals at high risk of PTSD, may enable targeted early intervention, initially as a PTSD prevention-screening device to minimise or prevent exposure to trauma (primary screen) and later for those trauma exposed to ascertain vulnerability to developing PTSD (secondary screening). The benefit of olfaction as a screening device is that it is reliable (consistency of scores on re-examination), is valid (measures olfactory performance on three levels) and is cost effective. Finally, an olfactory biological vulnerability marker for PTSD could facilitate diagnostic procedures, monitor the course of therapy, assist risk evaluation and provide further understanding of the development of PTSD.

Methods of Study

In order to investigate whether olfactory deficits predate the onset of PTSD in trauma survivors and to ascertain the viability of olfactory testing as a screening tool in predicting vulnerability to PTSD the following methods were used. A prospective cohort

study with a ‘between subjects’ and ‘within subjects’ design was used to compare the psychiatric and olfactory functioning of trauma victims with PTSD and trauma victims without PTSD over a 12 month period. Patients were selected from trauma admissions to the Royal Adelaide Hospital over a 24-month period. Traumatically injured patients were assessed during hospital admission (Time 1) and followed up at 3 months (Time 2) and 12 months (Time 3). Assessment of PTSD was with the Clinician-Administered PTSD Scale and Olfactory Functioning via the “Sniffin’ Sticks” method (Kobal, Hummel, Sekinger, Barz, Roscher and Wolf, 1996). Tests of olfaction included Threshold, Identification and Discrimination.

There were several limitations to the study. Although 202 participants were recruited to the study, by Time 3 there were only 146 participants. Unfortunately, missing data has the potential to distort the conclusions. However, despite multiple efforts to engage participants, reasons for lack of follow up included moving interstate or to the country, death, uncontactable, jail and voluntary withdrawal. Secondly, the duration of follow up was for 12 months only. This means that a great deal of olfactory data and information has been forgone. For instance, at what stage in the chronicity of PTSD does Olfactory Identification reduce from increased (as found in this study) to decreased as found in the studies of Vietnam veterans (Dileo, Brewer, Hopwood, Anderson and Creamer, 2008; Vasterling, Brailey and Sutker, 2000)?

Significant Findings

Despite the limitations, the objectives of the research were achieved as the results demonstrated that olfaction is a reliable marker of PTSD. This is both as a predictor of PTSD, thus demonstrating its utility as a biological vulnerability marker, and due to the effects of PTSD. Olfaction appears to be an excellent measure of sensitisation and reflects biological sensitisation and kindling. Specifically:

- High Olfactory Threshold at Time 1 is a predictive measure of PTSD at Time 2 and at Time 3 for females. Thus, females are more prone to PTSD if they have a high Olfactory Threshold but this relationship also existed for males at Time 2.
- High Olfactory Identification scores are significantly related to PTSD at Time 2 and Time 3.
- This suggests that individuals who demonstrate superior Olfactory Identification are at increased risk of conditioning and sensitisation and, following the onset of PTSD, experience a further escalation in olfactory acuity.

Implications

These results corroborate the ‘increasing sensitisation model’ of PTSD, which contends that PTSD is not an immutable, fixed condition, but dynamic, involving escalating neuropsychobiological processes (McFarlane, 2010). Due to the extensive shared neurophysiology of the limbic and olfactory systems, much of the escalating neuropsychobiological process can be observed via olfactory functioning. Consequently, olfaction becomes a window to the brain.

Thus, this study confirms the observation of a comorbid bidirectional relationship between trauma and sensitisation in the aetiology and development of PTSD. The significant relationship between olfaction and PTSD means that olfactory testing may have potential application in the screening and prevention of this disorder.

Chapter Synopsis

Chapter 1 presents the introduction. In this section, the relationship between PTSD and sensitisation is noted however, mechanisms are poorly understood. There are few biological vulnerability markers demonstrating sensitisation, which indicate vulnerability to PTSD. However, measures of olfaction have been reliable predictive markers in the development of neurological disorders and this may-be the case in PTSD. Thus, the objective of the study was to determine whether olfaction is a biological vulnerability

marker predicting PTSD. The results suggest a predictive comorbid bidirectional relationship between trauma and sensitisation as demonstrated by olfaction.

Chapter 2 contains the literature review. Firstly, it presents PTSD with its risk factors and sensitisation. Following this, olfactory anatomy and physiology is reported along with its relationship to the OFC. Olfactory dysfunction and the reasons for this are then described. The reasons presented in increasing order of specificity are: peripheral, central, developmental, neurodegenerative and psychiatric. Following this, olfactory disorder and PTSD are specifically examined with a stated rationale and hypotheses.

Chapter 3 describes the methods of enquiry noting the recruitment of participants, variables and measures, procedure, participant characteristics and analyses to be conducted. Chapter 4 states the results, provides descriptive results and analyses of Olfactory Identification, Discrimination and Threshold by PTSD. The results suggested that high Olfactory Threshold at Time 1 is a predictive measure of PTSD at Time 2 and at Time 3 for females. High Olfactory Identification scores are significantly related to PTSD at Time 2 and Time 3. Chapter 5 presents the significant results and a discussion of these findings. The study notes a predictive comorbid bidirectional relationship between trauma and sensitisation in the aetiology and development of PTSD.

CHAPTER 2: LITERATURE REVIEW

Background to PTSD

Brief History

The human response of those who have witnessed or experienced a major trauma has been of great interest to keen observers of human behaviour. Authors of ancient books such as the Bible, the Iliad and Shakespeare's Henry IV have recorded incidents of trauma and its concomitant aftermaths. For instance, Pepys who witnessed the great fire of London in 1666 described his behaviour and reactions in the aftermath of the blaze. He noted how an associated cue could trigger a re-experiencing of the trauma (Daly, 1983). Charles Dickens, who experienced a traumatic train crash and documented his subsequent reactions to it, attributed his symptoms to being shaken while being on a train. As many notorious accidents of that era involved the railway, some subsequent traumatic symptoms became described as 'spinal concussion' or 'railway spine' (Turnbull, 1998).

Another obvious and profound trauma is warfare. During the American Civil War, many soldiers began to present to physicians with autonomic cardiac symptoms and this syndrome became known as 'Soldiers Heart'. It was during this era that the belief began to develop that one could suffer psychological effects from exposure to serious trauma, which could then be categorised. For instance, the terms Nervous Shock, Shell Shock, Traumatic Shock, Traumatic Neurosis, War Neurosis and Battle Fatigue began to be used to describe PTSD like symptoms (Parry-Jones and Parry-Jones, 1994). During WWI the term 'Shell Shock' was used to describe soldiers with PTSD. Its aetiology was presumed to be because of brain trauma due to the repeated exposure of exploding shells. Later, WWII veterans who presented with similar symptoms to the veterans of WWI were being diagnosed as having syndromes such as 'Operational Fatigue' or 'Combat Neurosis' (Sadock and Sadock, 2003).

Simultaneously during this period, the scientific schools of physiology and behavioural psychology added a multidimensional focus by including biological, psychological and interrelated consequences of exposure to trauma. It was noted that there are unique biological changes in those who are exposed to trauma, which are quite different from other mental disorders (Pitman, 1989). The term Post Traumatic Stress Disorder was introduced by the scientific community after the Vietnam War with all of its associated morbidity and ratified in the ICD 9 (1978) and the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.; *DSM-III*; American Psychiatric Association, 1980).

DSM IV TR Diagnostic Criteria for Post Traumatic Stress Disorder

The criteria for Post Traumatic Stress Disorder as described by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000), are quoted verbatim from pages 467 – 468.

Diagnostic criteria for 309.81 Posttraumatic Stress Disorder

- A. *The person has been exposed to a traumatic event in which both of the following were present:*
- 1) *The person experienced, witnessed or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.*
 - 2) *The person's response involved intense fear helplessness or horror.*
- B. *The traumatic event is persistently reexperienced in one or more of the following ways:*
- 1) *Recurrent and intrusive distressing recollections of the event including images thoughts or perceptions*

- 2) *Recurrent distressing dreams of the event*
- 3) *Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated)*
- 4) *Intense psychological distress at exposure to internal or external cues that symbolise or resemble an aspect of the traumatic event.*
- 5) *Physiological reactivity on exposure to internal or external cues that symbolise or resemble an aspect of the traumatic event.*

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three or more of the following:

- 1) *Efforts to avoid thoughts feelings or conversations associated with the trauma*
- 2) *Efforts to avoid activities places or people that arouse recollections of the trauma*
- 3) *Inability to recall an important aspect of the trauma*
- 4) *Marked diminished interest or participation in significant activities*
- 5) *Feeling of detachment or estrangement from others*
- 6) *Restricted range of affect (e.g., unable to have loving feelings)*
- 7) *Sense of a foreshortened future (e.g., does not expect to have a career, marriage children or a normal life span)*

D. Persistent symptoms of increased arousal (not present before the trauma) as indicated by two (or more) of the following:

- 1) *Difficulty falling or staying asleep*
- 2) *Irritability or outbursts of anger*
- 3) *Difficulty concentrating*

- 4) *Hypervigilance*
- 5) *Exaggerated startle response.*

E. Duration of the disturbance (symptoms in Criterion B, C and D) is more than 1 month.

F. The disturbance causes clinically significant distress or impairment in social occupational or other important areas of functioning.

Specify if:

Acute: If duration of symptoms is less than 3 months.

Chronic: If duration of symptoms is 3 months or more.

Specify if:

With Delayed onset: If onset of symptoms is at least 6 months after the stressor.

Epidemiology

Following exposure to trauma, some people may experience symptoms of acute stress disorder (ASD). However, in order for a diagnosis of ASD to be made symptoms must last for at least 2 days and abate after 4 weeks. According to *DSM-IV-TR* should symptoms continue post 4 weeks and meet the full criteria for Post Traumatic Stress Disorder then a diagnosis of Post Traumatic Stress Disorder (PTSD) can be concluded (American Psychiatric Association, 2000).

PTSD has emerged as a world wide major public health concern especially in populations experiencing high levels of armed conflict (Davidson, 2000). An analysis of the data from the 2007 National Survey of Mental Health and Wellbeing of Australians

found an estimated 12 month prevalence rate of PTSD at 6.4% (Slade, Johnston, Oakley Browne, Andrews, Whiteford, 2009). In comparison, the 12 month PTSD prevalence rate in the United States is reported at 3.5% (Kessler, Chiu, Demler, Merikangas and Walters, 2005). However, the life time prevalence of PTSD in the United States is estimated at 8% of the general population with an additional 5% - 15% experiencing subclinical forms of the disorder (Sadock and Sadock, 2003).

A study conducted in Australia which examined the psychological sequelae of those admitted to a major metropolitan hospital suffering traumatic injury found that 10% were likely to have a primary diagnosis at both 3 and 12 months of PTSD and a further 10% with depression. A frequent comorbidity of PTSD is major depression (O'Donnell, Creamer, Pattison and Atkin, 2004). A more recent longitudinal Australian cohort study (Injury Vulnerability Study) examined the psychiatric sequelae of traumatic injury following hospital admission. The results indicated that at 12 months post injury, 31% were diagnosed with a psychiatric disorder and of these 6% were diagnosed with PTSD. Those with mild traumatic brain injury were found to have almost twice the rate of PTSD (Bryant, O'Donnell, Creamer, McFarlane, Clark and Silove, 2010).

Comorbidity

Physical Comorbidity

To date there is an extensive literature documenting the relationship between PTSD and self-report measures of physical ill health, physical health related functional status and health risk behaviours amongst returned war veterans and others (Mancino, Pyne, Tripathi, Constans, Roca and Freeman, 2006); (Dobie, Kivlahan, Maynard, Bush, Davis and Bradley, 2004); (Ford, Schnurr, Friedman, Green, Adam, and Jex, 2004); (Lauterbach, Vora and Rakow, 2005). Studies of returned Iraq war veterans have further confirmed these observations (Hoge, Terhakopian, Castro, Messer and Engel, 2007) with reports of

PTSD significantly associated with lower ratings of general health, increased sick leave and physical symptoms and high somatic symptom severity.

Beside self report measures other studies have demonstrated that PTSD is associated with an increased risk of coronary heart disease in older men. It is thought that the mechanism for this is due to increased levels of sympathetic activation and hypothalamic-pituitary-adrenal axis (HPA axis) dysregulation which is related to arterial damage and concomitant coronary heart disease (Kubzansky, Koenen, Spiro, Vokonas and Sparrow, 2007).

Other investigations have noted a relationship between diabetes and mental disorders such as depression and anxiety. Goodwin and Davidson (2005) conducted a study from the National Comorbidity Survey data of 5,877 noninstitutionalised individuals aged between 15 - 54 which was adjusted for sociodemographic differences. Results indicated a significant and potentially specific link between self-reported diabetes and PTSD. They noted that diabetes only showed specific associations with childhood neglect, but not with any other types of trauma. The results indicated that trauma during childhood was most strongly associated with diabetes during adulthood but the data does not indicate the order of events or other possible contributing factors.

Trief, Ouimette, Wade, Shanahan and Weinstock (2006) conducted a study of all veterans enrolled in primary care in upstate New York. Of the 73,270 veterans, 14,436 were classified as having diabetes, with 8% of these having PTSD. Vieweg, Julius, Fernandez, Tassone, Narla and Pandurangi (2006) retrospectively reviewed data from the Department of Veteran's Affairs in Virginia. They reported that obesity among male veterans with PTSD was far greater than the national average and treatment for hypertension, diabetes mellitus, and dyslipidemia correlated with BMI. Treatment with psychotropic medications was not found to contribute to this.

Another study by Kamoi, Tanaka, Ikarashi and Miyakoshi (2006) when examining the effect of a 2004 earthquake on 229 Japanese patients with endocrine disorders found that although the PTSD score for all patients was low, those with central diabetes-insipidus and Hashimoto's disease had a significantly higher score, while those with adrenal insufficiency had a significantly lower score. The authors hypothesise that these differences could be due to the degree of activity of the hypothalamic-pituitary-adrenal axis. For instance, in patients with adrenal insufficiency the HPA axis could have been inactivated by stress while those with diabetes and Hashimoto's could have been activated by stress.

Boscarino (2004) conducted an epidemiological study of 2490 Vietnam veterans and assessed the association between chronic PTSD and the prevalence of common autoimmune diseases. Results indicated that PTSD was associated with rheumatoid arthritis, psoriasis, insulin-dependent diabetes, and thyroid disease. Another study by David, Woodward, Esquenazi and Mellman (2004) assessed 93 Vietnam veterans admitted to a rehabilitation facility who were diagnosed with either PTSD or alcohol dependence. It was found that patients who were diagnosed with PTSD were significantly more likely to have a condition such as osteoarthritis, diabetes, heart disease, comorbid depression, obesity, and elevated lipid levels.

Weisberg, Bruce, Machan, Kessler, Culpepper and Keller (2002), conducted a study of 502 patients with an anxiety disorder to determine the extent of self-reported nonpsychiatric medical conditions. It was found that those with PTSD were significantly more likely to have a particular medical condition such as anaemia, arthritis, asthma, back pain, diabetes, eczema, kidney disease, lung disease, and ulcer. Finally, some earlier longitudinal studies of veterans such as that by Schnurr, Spiro and Paris (2000) and Ouimette, Cronkite, Henson, Prins, Gima and Moos (2004) noted that PTSD was

associated with cardiovascular, musculoskeletal, dermatological, gastrointestinal conditions and circulatory disorders even after controlling for other comorbid disorders.

Consequently the sheer number of studies which have associated PTSD with diabetes, obesity, cardiovascular disease, gastrointestinal disease and a host of other medical conditions, indicate that the long term sequela of PTSD is significant global health issues. This is not unexpected given that chronic severe stress has been linked to changes in hormone and thyroid functioning, hypothalamic-pituitary-adrenal axis dysregulation, higher T-cell counts, lower cortisol levels and lower natural killer cell activity all of which contribute to autoimmune disorders (Boscarino, 2004). Interestingly a study by Norman, Means-Christensen, Craske, Sherbourne, Roy-Byrne and Stein (2006) noted that posttraumatic symptoms, rather than PTSD diagnosis, may mediate the relationship between trauma and health. In that study when considering males, diabetes and arthritis was correlated with trauma history, however a diagnosis of PTSD mediated the correlation between arthritis and trauma but not diabetes. Conversely amongst females, digestive disease and cancer were correlated with trauma but PTSD was not found to mediate this interaction.

Thus, the relationship between poor health and PTSD is complex and not straight forward. PTSD could precipitate poor health and poor health could predispose for PTSD. However, a third factor may also cause both resulting in a partial association between the two factors. A substantial twin study examining PTSD and poor health status was conducted to determine whether there were other factors which contributed to both poor health and PTSD. The results indicated that part of this association between PTSD and poor health is partially due to familial confounding and sociodemographic factors. This confounding was found to be a common environmental effect (Roy-Byrne, Noonan, Afari, Buchwald and Goldberg, 2006). The authors note that they did not measure this variable but a variable such as childhood abuse contributes to both.

A criticism of many PTSD studies to date is that there has been no adjustment for other confounding factors such as comorbid mental disorder and sociodemographic factors. Thus, some of the long term physical sequelae of trauma may not be unique to PTSD. In order to control for this, a Canadian Community Health Survey comprising 36,984 participants conducted by Sareen, Cox, Stein, Afifi, Fleet and Asmundson (2007), examined the relationship between PTSD and physical illness. They adjusted for confounders such as mental disorder and sociodemographic influence. Their results were consistent with other studies, which indicated that PTSD is significantly related to chronic pain, suicidality, respiratory, cardiovascular and gastrointestinal diseases.

The reasons for the association between PTSD and physical illness are not yet fully understood. However, several hypotheses have been proposed and it is likely that a combination of these factors contribute to physical illness. Firstly, biological irregularities associated with PTSD such as:

- hypothalamic-pituitary-axis dysfunction (Yehuda, 2002)
- increased cardiovascular reactivity (Rabe, Dorfel, Zollner, Maercker and Karl, 2006)
- disturbed sleep physiology (Sheikh, Woodward and Leskin, 2003)
- noradrenergic dysregulation (O'Donnell, Hegadoren and Coupland, 2004)
- enhanced thyroid function and autonomic hyperarousal (McFarlane, 2000).

Secondly psychological factors such as:

- depression, hostility and irrational cognitions such as, 'the world is completely dangerous' and 'I am completely incompetent' (Foa and Cahill, 2001)
- feelings of shame, guilt, and self-blame (McNally, 2003).

Thirdly behavioural factors such as:

- smoking (Feldner, Babson and Zvolensky, 2007)
- alcohol abuse (Jacobsen, Southwick and Kosten, 2001).

Finally, pain which was a direct result of the trauma may serve as a constant reminder of the trauma thus maintaining arousal, fatigue and avoidance (Asmundson, Coons, Taylor and Katz, 2002).

Psychiatric Comorbidity

To date there have been many studies demonstrating that PTSD is a disorder which has significant psychiatric comorbidity. For example the National Comorbidity Survey conducted by Kessler, Sonnega, Bromet, Hughes and Nelson (1995) indicated that 88% of males and 79% of females with life time PTSD had another psychiatric diagnosis where PTSD was the principal disorder. Also 59% of males and 44% of females with PTSD reported three or more psychiatric diagnoses. The most frequently cited comorbid disorder was major depression with just under half of those with PTSD reporting it. In fact, PTSD was associated with a greater prevalence of all disorders examined. These included depression, mania, phobia, generalised anxiety disorder, drug and alcohol abuse / dependence and dysthymia. In this Survey PTSD was the primary diagnosis in the majority of instances where people developed affective and substance-use disorders and in the development of conduct disorder amongst females. Thus although a pre-existing psychiatric history is a risk factor in the aetiology of PTSD, it alone also contributes significantly to the development of other psychiatric disorders.

An Australian study conducted by Creamer, Burgess and McFarlane (2001) corroborated Kessler, Sonnega, Bromet, Hughes and Nelson's (1995) National Comorbidity Survey results. Using data acquired from the Australian National Survey of Mental Health and Wellbeing, they noted that 85% of males and 80% of females with PTSD had another psychiatric diagnosis. Amongst males a major depressive episode, generalized anxiety disorder, and substance abuse were the most commonly reported disorders, where-as amongst females, major depressive episode and generalized anxiety disorder were the most commonly reported. Using the same data Mills, Teesson, Ross and

Peters (2006) noted that approximately, 33% of those with a PTSD diagnosis also had a substance abuse disorder, and conversely 5.9% of people with substance abuse disorder had a diagnosis of PTSD. It was calculated by the authors that a diagnosis of either disorder increased the likelihood of acquiring the other by a factor of six.

A thorough chronological observation of the order of events over a protracted period is required to provide the clearest evidence of comorbidity. Presently it appears that substance use disorder is more likely to develop after the onset of PTSD and depression and anxiety disorders are more likely to precede a trauma thus contributing to PTSD. An Anxiety Sensitivity Index administered by Taylor, Koch and McNally, 1992 demonstrated very high levels of anxiety in persons with PTSD. Further evidence has demonstrated that anxiety sensitivity promotes the maintenance of PTSD symptoms (Fedoroff, Taylor, Asmundson and Koch, 2000; Keogh, Ayers and Francis, 2002). Anxiety sensitivity is also factor increasing the reported severity of long term pain (Asmundson and Norton, 1995; Asmundson and Taylor, 1996). A possible reason for this is that an increased awareness of autonomic arousal may increase the awareness or experience of somatic symptoms (Norton and Asmundson, 2003). Thus although acute stress reactions are considered to be normal reactions to trauma, it appears that PTSD becomes a pathological response which is determined by specific neurobiological dysfunction (Foa, Stein and McFarlane, 2006).

Schnurr, Friedman and Bernardy (2002) have suggested that because many psychiatric disorders share similar symptoms this may provide part of the explanation for such high comorbid rates observed in those with PTSD. For example, both PTSD and major depression share impaired concentration, sleep disturbance, and reduced interest in one's surroundings. In addition, other typical PTSD responses such as emotional detachment and restricted range of affect in PTSD may be misconstrued as depressed mood and psychomotor retardation in major depression. Other symptoms share common features with other anxiety disorders. For instance avoidance noted in both phobia and

PTSD; autonomic hyperarousal, impaired concentration, irritability, hypervigilance, exaggerated startle and insomnia noted in both PTSD and generalized anxiety disorder; autonomic hyperarousal and dissociation noted in both PTSD and panic disorder; and the heightened physiological and psychological reactivity noted in some with PTSD could be misconstrued as panic disorder. Thus, as various degrees of anxiety disorder and depression accompany PTSD, it makes formulating an accurate diagnosis difficult.

Finally, amongst those with serious mental disorder the risk of developing PTSD post trauma is greatly increased. Those with serious mental disorder and PTSD are approximately nine times more at risk for acquiring anxiety and psychotic disorders than those without PTSD (McFarlane, Bookless and Air, 2001). Thus PTSD is a complex disorder in that being diagnosed with it simultaneously increases the risk of acquiring another mental disorder and also having a pre-existing mental disorder increases the risk of acquiring PTSD.

Aetiology

Risk Factors

A number of risk factors for PTSD have been identified and include pretrauma (before trauma), peritrauma (during the trauma) and posttrauma (after the trauma) variables.

Pretrauma factors.

Low education.

A number of studies have now demonstrated that lower educational level is a risk factor for PTSD. For instance, results from the National Survey of Mental Health and Wellbeing (Australia) indicated that youth, low education, female gender and low socioeconomic status predicted Posttraumatic Stress Disorder after trauma (Rosenman, 2002). Studies examining the effect of terrorism on both Israeli and Arab populations have found that that amongst other factors, low education was a risk factor for the number of

traumatic stress related symptoms (Bleich, Gelkopf, Melamed and Solomon, 2006) as well as PTSD (Hobfoll, Canetti-Nisim, Johnson, Palmieri, Varley and Galea, 2008).

A review article summarising the PTSD literature on the terrorist attacks on New York City and Washington had similar findings to other studies in that female gender, low economic status, poor social support, low education and prior drug abuse were significant risk factors (Laugharne, Janca and Widiger, 2007). Comparable studies amongst Manhattan residents have obtained similar results (DiGrande, Perrin, Thorpe, Thalji, Murphy, Wu, Farfel and Brackbill, 2008). Finally, in a study of PTSD in unsuccessful pregnancy, Engelhard, van den Hout and Schouten (2006) found that PTSD was significantly associated with high neuroticism and lower educational level, and that those with a high education and low neuroticism had almost negligible risk for PTSD.

Lowered IQ

There have been a number of published papers, which have indicated that those with PTSD have lower IQ scores than their counter-parts who have also been involved in a trauma. The difficulty has been in determining whether a low IQ score predated the trauma and is thus a risk factor for PTSD or whether PTSD independently is associated with a lower IQ score, especially Verbal IQ; or whether both factors are equally valid. Vasterling, Duke, Brailey, Constans, Allain and Sutker (2002) posit that both factors occur.

The association between IQ and PTSD has been examined amongst Vietnam war veterans in studies where IQ test results were available at enlistment well before deployment. The results of these studies by McNally and Shin (1995) and Macklin, Metzger, Litz, McNally, Lasko, Orr and Pitman (1998) indicated that veterans with PTSD had lower test scores than veterans without PTSD. This result has been replicated in a study by Vasterling, Duke, Brailey, Constans, Allain and Sutker (2002) where Vietnam war veterans with PTSD were ascertained to have a lower estimated precombat verbal IQ score.

Other studies have examined the association between IQ and the risk of PTSD in children. A study by Silva, Alpert, Munoz, Singh, Matzner and Dummit (2000) found that the greatest predictor of resilience was high IQ. However, they concluded that a longitudinal study needed to be conducted to determine IQ prior to trauma before the potential deleterious effects of PTSD on cognitive functioning. A longitudinal study by Breslau, Lucia and Alvarado (2006) assessed children at age 6 years and followed them up till age 17 years. They found that those with an IQ score greater than 115 at age 6 had significantly less risk of having PTSD than those at or below the population average. It was thus concluded that high IQ was a protective factor to trauma exposed individuals. Another longitudinal study by Koenen, Moffitt, Poulton, Martin and Caspi (2007) found that low IQ at age 5 and antisocial behaviour and poverty before age 11, predicted PTSD after a traumatic event which occurred between the ages of 26 years and 32 years.

Pre existing mental disorder.

To date there have been a number of published studies where the authors have examined whether a previous history of mental disorder is a potential risk factor in the development of PTSD. PTSD commonly co-occurs with other psychiatric disorders and shares symptoms with major depressive disorders, anxiety disorders and substance abuse. Thus, it intuitively stands to reason that premorbid psychological characteristics such as mental disorder may predispose those who have experienced a trauma to developing PTSD. Research has verified that:

- preexisting depression (Blanchard, Hickling, Taylor, Loos, Forneris and Jaccard, 1996);
- anxiety and depression, prior history of mental health issues (Mason, Turpin, Woods, Wardrope and Rowlands, 2006);
- previous psychiatric treatment (Harvey and Bryant, 1999);
- childhood history of ADHD (Adler, Kunz, Chua, Rotrosen and Resnick, 2004);

- previous emotional problems (Ehlers, Mayou and Bryant, 1998);
- pre-existing phobic disorders, somatoform and depressive disorders (Perkonigg, Kessler, Storz and Wittchen, 2000);
- pre-existing anxiety disorders (Breslau, Davis, Peterson and Schultz, 1997)

all predispose one to PTSD after the experience of trauma.

Despite these results, conclusions must be tempered with the knowledge that the majority of comorbid mental health disorders develop secondarily to PTSD by at least one year (Perkonigg, Kessler, Storz and Wittchen, 2000).

Female gender.

An extremely robust finding in the study of PTSD has been the significantly higher rates of this disorder amongst females (Olf, Langeland, Draijer and Gersons, 2007). This result is despite females being exposed to proportionately fewer traumas (Seedat, Stein and Carey, 2005). Explanations such as the different rates of rape, sexual assault and domestic violence and younger age at time of trauma do partially account for some of the variance (Seedat, Stein and Carey, 2005). However, large prospective epidemiological studies such as the one conducted by Holbrook, Hoyt, Stein and Sieber (2002) have found that the association between PTSD and gender is still independent of the means of trauma and trauma related factors.

Hippocampus and stress.

The hippocampus has a crucial role in both learning and memory. Also during times of stress, it has a significant role in regulating hypothalamic corticotropin releasing factor (CRF) via the paraventricular nucleus of the hypothalamus which in turn stimulates the release of adrenocorticotrophic hormone (ACTH) by the anterior pituitary. The ACTH in turn stimulates the release of glucocorticoids by the adrenal glands. Glucocorticoid influences many bodily functions and in the brain, protracted exposure to stress results in a glucocorticoid dependent reduction in dendritic arborisation, neurogenesis and

hippocampal volume (McEwen, 2001). As neurons in the hippocampus express receptors for glucocorticoids it would appear that they have a direct effect (McEwen, Weiss and Schwartz, 1968). Thus, the hippocampus regulates a feedback loop with inhibitory afferents suppressing hypothalamic release of CRF. This means that the hippocampus is both the object and regulator of stress (Dranovsky and Hen, 2006).

Studies of those with PTSD consistently show hippocampal atrophy. A decrease in neurogenesis in the dentate gyrus together with atrophy and death of hippocampal neurons contributes to hippocampal attrition. Thus, factors which diminish hippocampal plasticity may promote vulnerability to PTSD in those who have experienced a major trauma. For instance, any condition which inhibits neurogenesis such as chronic stress as a child, nicotine dependence, alcohol dependence or age could possibly become a vulnerability factor or a factor in maintaining PTSD. Conversely, factors which promote neurogenesis may be neuroprotective and promote resilience to PTSD.

Nicotine dependence.

A host of studies have now reported a relationship between PTSD and nicotine dependence (Hapke, Schumann, Rumpf, John, Konerding and Meyer, 2005). A landmark study of a 6744 member twin registry examining the relationship between PTSD and nicotine dependence in male veterans was conducted by Koenen, Hitsman, Lyons, Niaura, McCaffery, Goldberg, Eisen, True, and Tsuang (2005). Firstly, they established an association between PTSD and nicotine dependence. These results reflected those obtained by Breslau, Davis and Schultz (2003) who earlier found that a diagnosis of PTSD increased the risk of nicotine and drug dependence. Following this Koenen, Hitsman, Lyons, Niaura, McCaffery, Goldberg, Eisen, True, and Tsuang (2005) controlled for a variety of shared risk factors and found that much of the association (63%) was accounted for by shared genetic factors. However, after accounting for shared genetic risk factors,

pre-existing nicotine dependence was associated with double the increased risk of developing PTSD if exposed to trauma.

Sleep.

Sleep disorder and mental disorder appear to be highly correlated. A World Health Organisation study by Ustun, Privett, Lecrubier, Weiller, Simon, Korten, Bassett, Maier and Sartorius (1996) of 5438 people in a general health care setting found that 51.5% of those with sleep difficulties had a mental disorder. Other studies such as that by Spoormaker and van den Bout (2005) have found a relationship between sleep disturbance, depression and anxiety. Other studies also demonstrate that dream content is affected by recent threatening experiences, with sleep disruption following trauma particularly prevalent amongst those developing PTSD. Subjective reports of those with PTSD indicate that 70% - 91% have difficulty initiating and maintaining sleep with many reporting nightmares (Maher, Rego and Asnis, 2006). Further studies by Germain, Buysse and Nofzinger (2008) and Mellman and Hipolito (2006) note that sleep disorder including nightmares and insomnia are core features of PTSD and consider that it is very likely to contribute to the production and development of the disorder including symptom severity.

A study by Spoormaker and Montgomery (2008) indicated that pre-existing sleep disturbance increases the risk for PTSD. Meerlo, Sgoifo, Suchecki (2008) have proposed a model whereby disrupted and reduced sleep contributes to the sensitisation of neuroendocrine and cardiovascular stress responses which perpetuates PTSD amongst those with the disorder.

Previous trauma.

According to Heim and Nemeroff (2001), there are many epidemiological studies which demonstrate that childhood trauma and significantly adverse experiences increase the risk for depression and anxiety disorders. There is also a plethora of studies such as those by Breslau, Chilcoat, Kessler and Davis (1999), Galea, Ahern, Resnick, Kilpatrick,

Bucuvalas, Gold and Vlahov (2002) and Bremner, Southwick, Johnson, Yehuda and Charney (1993) which have demonstrated elevated rates of prior trauma in adults who have PTSD in comparison to those who do not. However, a recent prospective epidemiological study by Breslau, Peterson and Schultz (2008) obtained results which indicated that prior trauma did indeed increase the risk of PTSD after a trauma but only amongst those who had acquired PTSD following the original trauma. Thus they considered that it was doubtful if one could state with certainty whether it was singularly the prior trauma or prior PTSD which increases the risk of PTSD after a subsequent trauma. They suggest that a pre-existing vulnerability to trauma may explain the PTSD response to both the prior and subsequent trauma.

Neuroticism.

For some time now it has been apparent that personality traits play a key role in the development of PTSD. McFarlane (1988) conducted a longitudinal study of fire fighters who were exposed to a bushfire disaster and found that among the premorbid variables which were associated with the development of chronic PTSD were introversion and neuroticism. These findings have been further replicated in many studies. For instance, a longitudinal cohort study of burns survivors found that those who developed PTSD in comparison to those who did not were characterised by high neuroticism and low extraversion scores (Fauerbach, Lawrence, Schmidt, Munster, and Costa, 2000).

A particularly large study using data collected from the American National Comorbidity Survey Part II (Cox, MacPherson, Enns and McWilliams, 2004) found that amongst those who had experienced a trauma, neuroticism was significantly associated with PTSD. Other studies examining PTSD in females after miscarriage or stillbirth found that amongst those high in education and low in neuroticism the risk of PTSD was almost negligible, however amongst those low in education and high in neuroticism the estimated risk was approximately 70% (Engelhard, van den Hout and Schouten, 2006). An

explanation for part of this association is that those who score highly on neuroticism are more likely to appraise ambiguous stimuli as more threatening and hence likely to increase post trauma (MacLeod and Cohen, 1993). For instance, a study of soldiers deployed to Iraq who developed PTSD symptoms found that those who were high in neuroticism were more likely to report PTSD symptoms to relatively minor stressors due to their appraisal of the situation (Engelhard and van den Hout, 2007).

Childhood trauma.

From the studies to date, childhood trauma and adversity emerge to be risk factors in the development of PTSD. A longitudinal community sample of children (N = 1420) who were followed up for 7 years found that very few children having been exposed to trauma developed post traumatic stress symptoms. However, those who were diagnosed with PTSD were more likely to be older, have been exposed to multiple traumas and had a history of anxiety or family adversity (Copeland, Keeler, Angold and Costello, 2007). However there are two factors very much related, which need to be considered when examining PTSD risk. First is the increased risk of exposure to trauma and secondly the increased risk of developing PTSD. This suggests that the risk of developing PTSD is not a randomly distributed occurrence. For instance a study by Koenen, Moffitt, Poulton, Martin and Caspi (2007) found that maternal distress, loss of a parent and family environmental stressors before age 11 significantly increased the risk of trauma exposure and PTSD when assessed at age 26. Other risk factors for developing PTSD were low IQ before age 5, poverty and antisocial behaviour before age 11. A meta-analysis of studies (N = 68) found that there was a small but significant risk of PTSD in those with a family history of psychopathology, prior trauma, and prior poor psychological adjustment (Ozer, Best, Lipsey and Weiss, 2003).

Research has suggested that one of the effects of trauma in children is subtle neurological changes in the brain. A longitudinal study by Carrion, Weems and Reiss

(2007) of children who had been maltreated found that PTSD symptoms and cortisol levels at baseline predicted hippocampal reduction over a period of 12 – 18 months. This finding suggests that stress may cause hippocampal impairment.

Peritrauma factors.

Trauma severity.

Logically a peritraumatic variable such as the actual magnitude of a trauma or the perception of the trauma will be a considerable predictor in the development of PTSD. Trauma severity was the only predictor of posttraumatic stress symptoms identified at both 3 and 12 months posttrauma in a study conducted by Carlier, Lamberts and Gersons (1997). Other studies have replicated these results with severity of exposure to the trauma being positively correlated to rates of PTSD (Norris, Friedman, Watson, Byrne, Diaz and Kaniasty, 2002; Stein, Seedat, Iversen and Wessely, 2007).

Dissociation.

Dissociation in the context of a trauma occurs when there is a divergence from usual awareness. The definition in *DSM-IV-TR* is, “The individual deals with emotional conflict or internal or external stressors with a breakdown in the usually integrated functions of consciousness, memory, perception of self or the environment, or sensory / motor behaviour” (American Psychiatric Association, 2000, p.811). Examples of dissociation include emotional numbing, a sense of detachment, reduced awareness of surroundings with the subsequent incomplete registration of events, derealisation i.e., time distortion, depersonalization i.e., experiencing the self as divided and dissociative amnesia (Bryant, 2007).

To date the majority of the literature on dissociation and trauma indicates that peritraumatic dissociation is a risk factor for PTSD. For instance, a meta-analysis of studies of peritraumatic dissociation by Breh and Seidler (2007) found that peritraumatic dissociation was a moderate risk factor for PTSD. Other cross sectional studies have found

that “the primary risk for PTSD is less whether one dissociates during (or soon after) a traumatic event than whether such dissociation persists over time” (Briere, Scott and Weathers, 2005, p. 2299). Other authors conducting prospective longitudinal studies have arrived at to similar conclusions (Murray, Ehlers and Mayou, 2002). Thus, it seems reasonable to conclude that continual dissociation is a significant factor in maintaining PTSD.

Finally, two authors have reported the non-linear nature of the association between dissociation and PTSD, Op Den Veldt, Arts, Shaken and Son (2006) and Bryant (2007). Bryant (2007) notes that it is likely to be more beneficial to deconstruct and examine the individual responses of awareness rather than treat dissociation as a global construct.

Posttrauma factors.

Alcohol abuse.

Apart from depression, alcohol dependence is the most common psychiatric disorder (Kessler, McGonagle, Zhao, Nelson, Hughes, Eshleman, Wittchen and Kendler, 1994) and PTSD is extremely common amongst those with alcohol dependence (Jacobsen, Southwick, and Kosten, 2001) and (Stewart, 1996). High rates of comorbid PTSD and substance abuse have been noted in a number of epidemiological studies with prevalence rates of comorbid PTSD and alcohol abuse estimated to range from 36 % - 52% (Kessler, Sonnega, Bromet, Hughes and Nelson, 1995). Thus, these high rates of comorbidity suggest that PTSD and substance abuse are functionally related to one another. Although many explanations have been proposed the causal trajectory remains unknown (Breslau, Davis and Schultz, 2003).

It is estimated that rates of PTSD amongst those who are alcohol dependent are twice those of the general population (Kessler, Crum, Warner, Nelson, Schulenberg, and Anthony, 1997). Those with both diagnoses of alcohol abuse and PTSD are more difficult

to treat as they typically have greater impairment than just PTSD or alcohol abuse alone (Back, Dansky, Coffey, Saladin, Sonne and Brady, 2000).

Many studies to date indicate that alcohol abuse became an issue after the initial occurrence of PTSD (Jacobsen, Southwick and Kosten, 2001). It is estimated that PTSD was the primary factor in comorbid PTSD and alcohol abuse in approximately 65.3% of males and 84.3% of females (Kessler, Crum, Warner, Nelson, Schulenberg, and Anthony, 1997). Another study by Epstein, Saunders, Kilpatrick and Resnick (1998) noted that amongst a national probability household sample of adult females in the United States, 65% reported the onset of PTSD before alcohol abuse symptoms. However as the Kessler et al. (1995) National Comorbidity Survey noted, alcohol dependence often predates the onset of PTSD.

A noteworthy longitudinal study by Port, Engdahl and Frazier (2001) who followed POW's from the Korean war and WWII found that aged veterans who were experiencing PTSD for the first time had higher lifetime rates of alcohol abuse and reported more health problems than their counter-parts whose symptoms remained below criteria. Other studies suggesting that alcohol abuse may contribute to the increased risk of developing PTSD or be associated with more severe symptoms include, Acierno, Resnick, Kilpatrick, Saunders and Best (1999) and Cottler, Compton, Mager, Spitznagel and Janca (1992).

Aging.

Many aging trauma survivors appear to be presenting with increased PTSD symptom rates and some who were previously asymptomatic are presenting with long delayed onset PTSD. Solomon and Mikulincer (2006) conducted a prospective longitudinal study of 214 veterans from the Lebanon war at 1, 2, 3, and 20 years post war. Results indicated that subjects in both groups those who initially suffered combat stress reaction and those who did not, had a fluctuating course of PTSD. PTSD rates declined 3 years post war and increased 17 years later. Among the veterans reporting no combat

stress reaction there was a 23% increase in delayed PTSD. Another study among older community dwelling and non-compensation-seeking male prisoners of war found that PTSD prevalence rates and symptoms were most acute immediately after the war then abated for several decades then re-emerged within the last two decades of their life (Port, Engdahl and Frazier, 2001). An Australian case study investigated the delayed onset of PTSD amongst 15 elderly Australian combat veterans. Results indicated that in the majority of subjects PTSD symptoms were connected to psychosocial stress, unrelated medical ailments and or minor cognitive impairment (Ruzich, Looi and Robertson, 2005).

It is possible that the combination of stressors, neurological decline and cessation of neurogenesis may have precipitated a latent onset of PTSD in combat survivors. These findings are similar to those of Herrmann and Eryavec (1994), who noted that delayed onset PTSD was associated with late life stress such as a chronic medical condition, social isolation and grief over the loss of loved ones.

Poor social support.

Lack of social support is an important risk factor in the development of PTSD as indicated in a meta-analysis by Brewin, Andrews, and Valentine (2000). Another meta-analytical study replicated the above results and found that lack of social support was one of the main predictive factors for PTSD (Ozer, Best, Lipsey and Weiss, 2003). The finding that social support is a factor in the development and maintenance of PTSD is very robust and current studies with more diverse populations have demonstrated similar results. For instance a study which examined the mental effects of disasters such as hurricanes found that a high degree of social support six months prior to the event was a protective factor against anxiety disorders, depressive disorders and PTSD (Acierno, Ruggiero, Galea, Resnick, Koenen, Roitzsch, de Arellano, Boyle and Kilpatrick, 2007).

Another study which examined predictors of chronic PTSD amongst facially injured socioeconomically disadvantaged found that one of the salient predictors was poor

social support (Glynn, Shetty, Elliot-Brown, Leathers, Belin and Wang, 2007). A very large study of inner city females who had been sexually assaulted found that those who had been abused as children and sexually assaulted as adults had very high rates of PTSD. However, amongst those with a high rate of social support the development and severity of PTSD was significantly mitigated (Schumm, Briggs-Phillips and Hobfoll, 2006).

Studies on the rates of PTSD post tsunami have found that adolescents who had positive mother child relationships had less PTSD and depressive symptoms while conversely those adolescents whose mothers were depressed and therefore not as available to provide support suffered more detrimental mental health effects (Wickrama and Kaspar, 2007). Others survivors who remained resilient post tsunami were those identified as support seeking while those with poor adjustment were noted to be infrequent support seekers (Tang, 2006).

These findings demonstrate that lack of social support is an important factor in the development of PTSD. Thus, an important aspect of psychotherapeutic intervention is to assist the survivor to cultivate, maintain and promote appropriate social support and strengthen existing supportive networks.

Ensuing life stress.

An interesting longitudinal study (N = 2,548) examining remission and chronicity of PTSD in German adolescents and young adults was conducted by Perkonigg, Pfister, Stein, Hofler, Lieb, Maercker and Wittchen (2005). They found that those who endured chronic PTSD were significantly more likely than their counter-parts in remission to be exposed to further trauma during the follow up period of the survey. Another study investigating PTSD amongst veterans found that several factors including a history of post military assault was associated with PTSD severity (Clancy, Graybeal, Tompson, Badgett, Feldman, Calhoun, Erkanli, Hertzberg and Beckham, 2006). Other populations which have also been investigated include community mental health. Although only a small

study, those in this population with a dual diagnosis including PTSD reported twice the rate of trauma exposure in comparison to those without PTSD (Howgego, Owen, Meldrum, Yellowlees, Dark and Parslow, 2005).

Thus it appears that those who have been traumatised and subsequently experience another trauma are more likely to suffer either PTSD or chronic PTSD. However, this relationship is not entirely one directional. A study of returning Gulf war veterans found that direct combat experience significantly increased the risk that veterans would experience another trauma in the two year period upon return to the USA. The authors note that in this study PTSD symptomatology mediated 48% of the total effect of combat exposure in the relationship between trauma and further trauma exposure (Orcutt, Erickson and Wolfe, 2002).

Threat to safety.

It has been reported in the literature that ongoing threat to safety is a risk factor in the development of PTSD. For instance, a study examining the effects of war in former Yugoslavia found that the fear of threat to safety and loss of control of life were mediating factors in the development of both PTSD and depression (Basoglu, Livanou, Crnobaric, Franciskovic, Suljic, Duric and Vranesic, 2005). Other studies have found that lower perceived safety was a small risk factor in the diagnosis of ASD (Grieger, Fullerton, Ursano and Reeves, 2003). However, a study by Grieger, Fullerton and Ursano (2004) indicate that this association may not be linear but possibly circular. In that study the relationship between PTSD and survivors of the terrorist attack on the Pentagon staff was assessed. As expected, those directly exposed to the attack were more likely to have PTSD and depression. They also had a perception of low levels of safety at work, usual activities and travel, but did not feel unsafe at home. However in contrast to the above group who were directly exposed to the attack, those with PTSD reported a perception of low levels of safety at work, usual activities, travel and significantly, at home. The authors conclude

that PTSD has an influence on global perceptions of safety and that threat to safety is both simultaneously a risk factor in the development of PTSD and a consequence of its effect.

Although there are a number of listed risk factors not all have the same predictive effect. They vary according to populations being assessed and when they occur. Stam (2007) notes that all of the risk factors combined only account for approximately 20% of PTSD outcome whilst the remainder is a combination of unknown factors, individual response, personality variables e.g., neuroticism (McFarlane, 1989) and circumstances of the trauma. Brewin, Andrews and Valentine (2000) combined all of the effect sizes in their meta study in order to determine the strength of each predictive factor. They found that individually the effect size of all risk factors was modest but that peritrauma and post trauma factors were the most influential. After combining effect sizes, the strongest risk factors in order were: 1) lack of perceived social support; 2) subsequent life stress; 3) trauma severity; 4) adverse childhood; 5) low IQ.

PTSD and Sensitisation

Symptoms of PTSD frequently include intrusive memories of the traumatic event, flashbacks and a hyperavoidance of stimuli or situations associated with the original trauma. Persistent physiological symptoms of hyperarousal, hypervigilance and insomnia are often reported by those suffering PTSD (Forbes, Parslow, Creamer, O'Donnell, Bryant, McFarlane, Silove and Shalev, 2010) and are part of the diagnostic criteria. Criterion D5 in the *DSM-IV-TR* of PTSD is an exaggerated startle response (American Psychiatric Association, 2000) and it is this increased startle reactivity, which is indicative of hyperarousal. This is a common physiological response amongst those with PTSD and is to be found amongst Vietnam veterans with PTSD (Butler, Braff, Rausch, Jenkins, Sprock and Geyer, 1990). Other studies have obtained similar results. Griffin (2008) conducted a study of startle reactivity amongst 40 sexual assault survivors. He found that there was no difference between the PTSD and non PTSD groups at one month. However, six months

later the PTSD group had an increased startle response from the one month response and a significantly greater startle response than the non PTSD group. This result indicated that it appears that the startle response develops over time.

Research by Shalev, Peri, Brandes, Freedman, Orr and Pitman (2000) has demonstrated elevated autonomic responses to startling tones in trauma survivors with PTSD. This particular prospective study found that the heightened physiological responses to a startle tone developed following exposure to the traumatic event. Thus they concluded that their results supported the hypothesis, PTSD promotes progressive neuronal sensitisation. However, another prospective study by Guthrie and Bryant (2005) evaluated the auditory startle response in fire fighters both before and after trauma exposure. Their results found that pretrauma physiological reactivity was predictive of posttrauma acoustic startle responses which were themselves predictive of posttraumatic stress severity. They subsequently concluded that pretrauma physiological reactivity as demonstrated by the elevated startle response is a vulnerability factor for PTSD. Either way the findings from both of these studies indicate that those with PTSD process stimuli from the environment in a different manner from those without PTSD.

However the vexing question remains. Do those with PTSD process stimuli in a different way due to pre-existing vulnerability factors, or as a direct result of the trauma, or as a combination of both. These distinctions are very difficult to make if they can be made at all. For instance, complicating factors such as exposure to prior trauma is a predictor of PTSD and this may be the reason why some are vulnerable or predisposed to PTSD as they have become increasingly sensitised due to previous dysregulation of arousal.

McFarlane, Clark, Bryant, Williams, Niaura, Paul, Hitsman, Stroud, Alexander and Gordon (2005) have noted the significant effect that a history of serious early life stress has on the developing brain, its functioning and resultant personality traits. They found abnormalities in electrical brain function via electroencephalography (EEG), increased

scores on the Depression Anxiety Stress Scales (DASS) and higher levels of neuroticism. Abnormal event-related potentials have also been noted to occur in those who suffer PTSD (Galletly, Clark, McFarlane and Weber, 2001). Recent research using quantitative electroencephalography (qEEG) has found basal instability of cortical arousal in those suffering anxiety related disorders (Clark, Galletly, Ash, Moores, Penrose and McFarlane, 2009).

Thus, it has been suggested by those who have proposed the stress sensitisation hypothesis, that childhood adversity may be a mechanism by which vulnerability to mental illness is increased following adult stressful life events. In order to test this stress sensitisation thesis an epidemiological survey of 34, 653 adults was conducted by McLaughlin, Conron, Koenen and Gilman (2010). Their results supported the hypothesis and noted a correlation between the preceding year stressful life events and a significant increase in the risk of major depression, PTSD and other anxiety disorders. However, the extent of the increase in risk was dependent on the degree of childhood adversity. Those reporting three or more childhood adverse events demonstrated the greatest stress sensitisation. The other finding of interest was that females required fewer major events to trigger a stress sensitisation effect than males in relation to PTSD.

Of the many studies that have been conducted where early life stress and adversity have been examined the overwhelming consensus is an increased risk in adult psychiatric sequelae. Clark, Caldwell, Power and Stansfeld (2010) conducted a 45-Year Prospective Epidemiologic Study examining childhood adversity which they concluded was associated with adolescent, early adulthood, and midlife psychopathology. Fergusson, Boden and Horwood (2008) studied a New Zealand cohort to the age of 25 and found that children sexually abused were 2.4 times more likely than those not abused to have a psychiatric disorder. Those who had endured abusive physical treatment as children were 1.5 times more likely to experience mental health issues in comparison to those who did not.

Similarly, the rates of depression in females suffering abuse as an adult only, are significantly lower than those abused as an adult and child (Heim, Newport, Mletzko, Miller and Nemeroff, 2008). These results indicate that there appears to be a critical period of time when the effects of trauma have a more profound effect than at others. Rodrigues, Leao, Carvalho, Almeida and Sousa (2011) contend that stress induced high levels of glucocorticoids during pre and early post natal development affect dopamine transmission in the mesolimbic, mesocortical, and nigrostriatal systems. The changes are mostly determined by the state of brain development at the time of stress exposure.

Thus, it is becoming increasingly evident that early life stress is a significant vulnerability factor for adult mood and anxiety disorders. Major stress has been shown to have an enhanced or attenuated effect on corticotropin-releasing hormone (CRH) and hypothalamic-pituitary-adrenal axis function (Heim, Newport, Mletzko, Miller and Nemeroff, 2008). Due to the HPA axis being a significant physiological system which influences the response to stress, any fundamental adaptation by the HPA axis will affect future health. Thus a dysregulated HPA response can become established and continue long after a trauma event with the result that an individual may become hypersensitive to future fearful events. Previous clinical studies have verified that a dysregulated HPA axis is a vulnerability marker for depression (Holsboer, Lauer, Schreiber and Krieg, 1995).

Other studies by Duman and Monteggia (2006) note that continued or excessive exposure to stress and glucocorticoids alters the neurostructure of the limbic system which may well contribute to the development of stress-related disorders. The HPA axis is efficiently regulated by glucocorticoid inhibition via two corticosteroid receptors, namely the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). These receptors have an effect on the functioning of the pituitary, hypothalamus and hippocampus. Information about the current physical and psychological state accumulates on the HPA axis, which in turn releases cortisol which determines the physiological

response. The magnitude of the HPA response to stress thus depends upon the pre-existing glucocorticoid tone (Buckingham, Loxley, Christian and Philip, 1996).

When an individual experiences a significant stressor the immediate physiological response is the production of corticotrophin-releasing factor in the hypothalamus. This then in turn binds to specific receptors in pituitary cells which respond by producing adrenocorticotrophic hormone (ACTH). ACTH circulates throughout the limbic system to the adrenal glands which in turn responds by secreting cortisol. Cortisol is a steroid hormone or glucocorticoid which is secreted in response to stress and anxiety and functions to increase blood sugar levels, suppress the immune system and assist in the metabolism of carbohydrate, fat and protein. Its purpose is to enhance recovery by restoring physiological homeostasis after threat or challenge (Yehuda and McEwen, 2004). Cortisol has a metabolic effect for improving the stress response and functions through negative feedback to both the anterior pituitary and hypothalamus after the stress response has subsided. The process is complex and the stress response varied. Cortisol is elevated during stress but under severe stress is decreased and insufficient cortisol signalling is considered to be part of the PTSD process (Raison and Miller, 2003).

Thus, once the HPA axis has become chronically dysregulated (often hypercortisolism) and established due to serious early life stress, the result is that there is a marked increase in the risk for mental disorder. This also includes traumatisation and PTSD. It is likely that for many who are experiencing PTSD in adulthood it is as a result of the continuation of the stress response of early life stress (Vreeburg, Hoogendijk, van Pelt, Derijk, Verhagen, van Dyck, Smit, Zitman and Penninx, 2009). Yehuda, Flory, Pratchett, Buxbaum, Ising and Holsboer (2010) have noted that there are a number of neuroendocrine similarities between PTSD and the early life stress response; including reduced cortisol signalling and glucocorticoid receptor responsiveness. Aardal-Eriksson, Eriksson and Thorell (2001) conducted a study where they assessed salivary cortisol levels

and traumatic stress in soldiers following a severe incident. They found that when tested five days after the incident, soldiers reporting substantial posttraumatic distress also displayed significantly lower morning and higher evening cortisol levels in comparison to the low-impact group. Ehring, Ehlers, Cleare and Glucksman (2008) concluded after their research that there is a reduced cortisol response in the peri and immediate post traumatic period, which contributes to dysregulation of the sympathetic nervous system in those who develop PTSD. These findings support earlier research noting HPA axis dysfunction shortly after trauma in those who develop PTSD (McFarlane, Atchison and Yehuda, 1997).

Other studies have also noted that those with PTSD exhibit different biochemical outcomes from those with depression. For instance, those diagnosed with PTSD respond more robustly to the dexamethasone suppression test and with greater sensitivity to glucocorticoids than individuals with depression (Yehuda, Halligan, Golier, Grossman and Bierer, 2004). Yehuda (2001) contends that because of the strong cortisol suppression to dexamethasone in those suffering with PTSD it seems apparent that HPA axis dysregulation is due to established negative feedback inhibition of cortisol. Thus, a pathophysiological explanation of PTSD includes a maladaptive learned fear response via the hypersensitive, hyperresponsive and hyperactive HPA axis (Yehuda, 2002).

One of the significant features of the maladaptive learned fear response is progressive generalization whereby an individual responds in the same manner to similar stimuli. This creeping sensitisation to small stimuli is occurring at the same time as the neurohormonal response to trauma. This has been demonstrated by larger heart rate responses to sudden, loud startling tones. The literature had been divided for some time as to whether this was due to PTSD or a pretrauma vulnerability factor. The study by Orr, Metzger, Lasko, Macklin, Hu, Shalev, Pitman and Harvard/Veterans Affairs Post-traumatic Stress Disorder Twin Study Investigators (2003) by recruiting monozygotic twins

discordant for combat exposure determined that the larger heart rate responses to sudden, loud tones were due to acquired PTSD rather than a familial vulnerability factor.

Thus, it is apparent that there is a post trauma period where the HPA axis becomes dysregulated in those with PTSD and brain plasticity increases (Shalev, 2000). These conditions combined with changing environment, aging and life stressors all coalesce to create a dynamic prerequisite necessary for delayed onset PTSD (McFarlane, 2010).

The Olfactory System

Anatomy and Physiology

The sense of smell has been the cause of speculation and fascination over eons of time as it is the most evocative and mysterious of our senses. It enlightens us as to the chemical composition of our environment (Firestein, 2001), endows food and beverages with flavour, provides aesthetic appeal and serves as an early warning mechanism. For instance, the smell of putrefying food is so obnoxious that we avoid it and other dangerous chemicals in the environment (Doty, 2001). There are two main olfactory systems which have been identified. Firstly the vomeronasal organ which performs a more minor role and secondly the far more dominant olfactory system which includes the epithelium and is responsible for the detection and discrimination of a vast plethora of odours (Breer, Fleischer and Strotmann, 2006).

We are particularly influenced by smells even unconsciously. Smells evoke emotions, memories and have an enormous influence on mood, social and sexual behaviour. For instance, the olfactory system not only identifies food but also contributes greatly to our enjoyment of it. Smell has a profound effect on the experience and taste of food, as we can in reality only taste bitter, salty, sour or sweet, so that ultimately all the flavours are because of smell. If blind folded and with noses pinched we could scarcely differentiate between a banana and a cucumber. In fact, it is considered that approximately 80 - 90% of what is actually perceived as taste is due to the sense of smell (Van Boekel,

2006). Thus, those complaining of a loss of taste frequently have significant olfactory deficits (Deems, Doty, Settle, Moore-Gillon, Shaman, Mester, Kimmelman, Brightman and Snow, 1991). It is now considered that humans are able to differentiate approximately 10,000 different odours and also at very low thresholds; for example such as at concentrations as low as a few parts per trillion (Shepherd, 2004). However, this sense of smell is still less developed in humans than in some other mammals such as rodents. Thus, the sense of smell is sensitive and specific and has been discovered to be as complex as the immune system.

Sniffing.

In mammals the act of smelling especially when odours are at low concentrations or when discriminating between odours, involves sniffing, which is an essential and complex behaviour in the entire process. It involves the conscious act of imbibing small but rapid amounts of air via nasal inhalation and provides an adequate air flow and transports volatile chemicals from the environment to the olfactory epithelium (Mainland and Sobel, 2006). There are substantial differences in air flow over the epithelium between resting respiration and active sniffing (Zhao, Dalton, Yang and Scherer, 2006) with increased velocity and changes in duration of airflow (Scott, 2006). Typically 15% of inspired air passes the epithelium (Hadley, Orlandi and Fong, 2004) but sniffing increases turbulence in the airflow and this is likely to increase odour sorption which is also dependent on molecule volatility and water solubility (Schoenfeld and Cleland, 2005). As olfactory receptor neurons are not uniformly distributed along the inspiratory axis it means that the number of air borne molecules binding to receptor neurons varies during a sniff. Thus by regulating and varying the sniff, odours can be further analyzed and modified via odour access to receptor neurons (Schoenfeld and Cleland, 2005).

Vomeronasal organ.

The vomeronasal organ exists in amphibians, reptiles (albeit not in crocodiles), and mammals. It is absent in birds and fishes (Trotier and Doving, 1998). In most mammals, it is located just above the roof of the mouth (Kambere and Lane, 2007). This organ is a particularly specialised olfactory system, which is considered to detect pheromones. Pheromones provide information about the social, gender, fertility and sexual status of individuals within the same species (Mombaerts, 2004; Hildebrand and Shepherd, 1997). Although this information gathering and assimilation is unconscious, it nevertheless shapes the autonomic psychological and endocrine systems through a different projection to the brain (Buck, 2004). Based on animal research, it is hypothesised that the vomeronasal organ in the human may contribute to the selection of a sexual partner (Bhutta, 2007).

Trigeminal nerve.

The fifth cranial nerve is the trigeminal nerve, which innervates the nose and face. This includes the cornea, conjunctiva of the eye, skin sensations from most of the face, control of jaw muscles for chewing and swallowing, oral and nasal cavities and also identifies noxious caustic odours such as ammonia. The vast majority of odours do have a trigeminal component to them, which ranges from mild to intense (Wysocki, Cowart and Radil, 2003). Even people suffering anosmia are able to differentiate odours because of trigeminal sensitivity (Laska, Distel and Hudson, 1997). However, it is very difficult to distinguish whether a particular odour sensation is originating from the olfactory or trigeminal system. Once activated the trigeminal nerve induces a reflexive response such as secretion of mucus and a catching of breath and somatosensory sensations such as irritation, cooling, warming, burning and stinging from the nasal mucosa via nociceptors and mechanoreceptors (Hummel, 2000). This is the reason for particular smells having a certain sensation to them, such as temperature and pungency.

The elicitation of a sharp and noxious trigeminal response by an odour may also contribute to the reason why some odours are immediately spurned. However, what trigeminal stimulation is precipitated is dependent on stimulus and site. For instance the sensitivity to mechanical stimulus such as a puff of air via mechanoreceptors is greatest in the posterior area of the nasal fossa, while the perception of chemosensory stimuli via nociceptors are more likely to be activated in the anterior area of the nasal cavity (Frasnelli, Heilmann and Hummel, 2004). The trigeminal and olfactory nerves share the same innervation areas in the nasal cavity and appear to function in an interactive way (Livermore and Hummel, 2004). As a result loss of olfactory function leads to a decreased trigeminal sensitivity, as indicated by anosmic subjects (Hummel and Kobal, 1992) and trigeminal stimuli may be perceived as more intense when accompanied by olfactory stimulus (Hummel, 2000). However, a decrease of trigeminal sensitivity in subjects with olfactory loss is specific to chemosensory sensation and not to mechanical stimulus (Frasnelli, Schuster, Zahnert and Hummel, 2006).

Olfactory epithelium.

Once an object such as fruit has released volatile odorous molecules into the air, they reach the nose and are inhaled into the nasal cavity. Once there, they are directed toward the olfactory sense organ, the olfactory epithelia. This is a mucus membrane composed of an epithelium and a subepithelial lamina propria of connective tissue, blood vessels and glands. It is located on the undersurface of the cribriform plate, which is in the upper posterior region by the turbinates or nasal conchae. Although the olfactory epithelium has an average surface area of only one square cm on either side of the nose, it contains more than 100 million olfactory receptor cells. This number of receptors is more than we have for all of the other senses excluding sight. However, as we age the olfactory epithelium does reduce in size due to the gradual replacement with nonolfactory

epithelium. This phenomenon is thought to be a major reason for the diminution of olfactory acuity with age (Hadley, Orlandi and Fong, 2004).

These specialised epithelial cells become part of the olfactory vesicles comprising kinocilia, which become locations for the transduction of stimuli. Neuronal activation occurs when odiferous molecules contact with olfactory vesicles. Incredibly olfactory epithelial cells undergo continual neurogenesis, a process where new neurons are continually generated throughout life. The life cycle of the 30 million olfactory cells from stem cell to mature functioning neuron is anything from weeks to months.

The olfactory epithelium is composed of three cell types; supporting, basal and olfactory sensory neurons. The supporting cells are spread amongst the olfactory sensory neurons and have multiple microvilli and secretory granules. The secretory granules discharge their contents onto the mucosal surface. The basal cells or neural stem cells are the cells, which continually generate either support cells or olfactory sensory neurons that are continually in the process of turning over. Olfactory sensory neurons or cells are bipolar neurons. They extend a single thin dendritic rod to the surface of the olfactory epithelium from where 5 - 20 highly specialised cilia are embedded in the protecting nasal mucus forming a matrix, which provides the transduction surface for odour molecules. Because of these cilia, the functional surface area of the epithelium is considerably expanded and estimated to be 22 square centimetres (Doty, 2001).

The cilia cell membrane contains receptor proteins (Strotmann, Levai, Fleischer, Schwarzenbacher and Breer, 2004) and other substances, which are part of the initiation of olfactory transduction (Menco, Bruch, Dau and Danho, 1992) where the chemical odour stimulus is converted into an electrical signal in the cell. These small olfactory odour receptor cells have a long central single unbranched unmyelinated axon. These axons gather in bundles in the lamina propria and course both superiorly and posteriorly, gathering into larger fascicles which form the fine fibres of the first cranial nerve and

project centrally toward the ipsilateral olfactory bulb to connect with the second-order neurons.

All olfactory sensory neurons have odour receptors which detect odour molecules. The olfactory sensory neurons express only one olfactory receptor type each, of which there are between 300 and 400 in humans and 1000 in mice (Buck, 2004). Yet there is a vast number of odours which humans perceive. The reason why it is possible for so many odours to be identified is because one odour receptor can recognise multiple odour molecules and one odour is recognised by multiple odour receptors (Malnic, Hirono, Sato and Buck, 1999). This means that different odorants are identified due to individual odour molecules activating distinct combinations of olfactory receptors and as a result are able to generate a monumental number of combinatorial receptor codes that define odorant identity. In order to enhance this process, different types of olfactory sensory neurons are expressed almost randomly in different zones of the epithelium and are arranged orthogonally to airflow. This creates an interaction between sensory specificity and chromatographic separation of odours across the nasal mucosa. This interaction assists to promote a unique activation pattern evoked by the various odour molecules (Schoenfeld and Cleland, 2005). Also slight alterations in an odorant, or change in its concentration, can change its code, possibly explaining how such changes can alter perceived odour quality (Malnic, Hirono, Sato and Buck, 1999). Therefore, by varying the sniffing response and rate, odours are more accurately identified and discriminated.

The distance from the olfactory epithelium in the nose to the olfactory bulb in the brain is very short and is the thickness of the cribriform plate. All olfactory sensory neurons which express the same odour receptors project their axons through the cribriform plate to common odour specific glomeruli in the olfactory bulb (Mombaerts, Wang, Dulac, Chao, Nemes, Mendelsohn, Edmondson and Axel, 1996). This convergence of odour receptor specific neurons onto odour receptor specific glomeruli produces a stereotyped

sensory map. A unique feature of the olfactory system is that these projections from the epithelium to the olfactory bulbs are ipsilateral. This means that the right nostril projects directly onto the right olfactory bulb and the left nostril projects directly onto the left olfactory bulb with no crossover to the contralateral hemisphere. However, at the level of secondary projections whilst the majority of olfactory information remains ipsilateral a small percentage crosses to the contralateral hemisphere via the anterior commissure (Eslinger, Damasio and Van Hoesen, 1982).

Cribriform plate.

The cribriform plate of the ethmoid bone is separated at the midline by the crista galli and contains numerous tiny foramina or sieve like holes through which the olfactory nerve fibres or fila olfactoria pass. Much olfactory dysfunction is because of the shearing of the olfactory fila as they pass through the cribriform plate (Collet, Grulois, Bertrand and Rombaux, 2009). This can occur during brain movement in contre coup or coup forces or even severing and crushing of the olfactory fila due to fracture of the cribriform plate (Reiter, DiNardo and Costanzo, 2004).

Olfactory bulb.

The olfactory bulbs which are located inferiorly to the basal frontal lobe are the first relay in the olfactory system and are essential to the detection and discrimination of odorants. They are particularly highly structured and are composed of five different divisions and corresponding synaptic specializations. The layers from the outer exterior to the centre are the: glomerular; external plexiform; mitral cell; internal plexiform; and granule cell.

Upon entering the olfactory bulb the axons from the olfactory nerve fibres defasciculate and enter specialised divisions. The outer exterior circumference of the olfactory bulb is the glomerular layer, which consists of dendritic arborisations (glomeruli) of the mitral cell, periglomerular cells and olfactory nerve fibers. Within the glomeruli,

periglomerular cells have multiple contacts with mitral cell dendrites and are able to impart inhibition of adjacent glomeruli while allocating excitation of a specific mitral cell dendritic tree. Each mitral cell is connected to at least 1000 olfactory nerve fibres thus achieving a high degree of convergence (Breer, 2008).

The external plexiform layer of the olfactory bulb includes the dendrites of bypassing mitral cells and tufted cells. Although less in number tufted cells receive granule cell input via dendrites. Selected granule cell dendrites in the plexiform layer contact mitral cell dendrites via a particular dendrodendritic synapse. This is termed a reciprocal synapse as vesicles are observed both within presynaptic and postsynaptic membranes. The largest neurons in the olfactory bulb are the pyramidal mitral cells, which are found in a thin layer at the boundary of the external plexiform layer and granule cell layer. At the plexiform layer, multiple neurotransmitters are involved in cell interactions, although glutamate is the principal neurotransmitter amongst olfactory receptor neurons (Huart, Rombaux and Hummel, 2013).

Second order neurons in the olfactory bulb known as mitral cells synapse with olfactory receptor neurons to form the glomerular layer of the bulb. Mitral-layer neurons of the olfactory bulb send olfactory information to higher brain centres, including the piriform cortex (PC), anterior olfactory nucleus (AON), amygdala, and hypothalamus (Komiya and Luo, 2006); (Mori, Takahashi, Igarashi and Yamaguchi, 2006). The internal plexiform layer is a thin layer of short axon cells, axons of principal cells and peripheral dendrites of granule cells. At this level, the granule cells comprise numerous neurons, which lack axons, but possessing extended dendritic processes are able to contact the more external layers and therefore inhibit mitral and tufted cells.

Physiologically the olfactory bulb maintains the pattern of input from the olfactory epithelium. Each olfactory epithelial sensory neuron can express only one type of odorant receptor gene from a possible 300 (Buck, 2000; Glusman, Yanai, Rubin and Lancet,

2001). The epithelium can be roughly divided into four spatially distinct zones of gene expression. But epithelial olfactory sensory neurons expressing the same odorant receptor are essentially randomly distributed across the epithelium. However, upon projecting to the olfactory bulb the axons converge to a specific set of glomeruli. Thus, each glomerulus is activated by olfactory neurons expressing only the one receptor gene (Mombaerts, Wang, Dulac, Chao, Nemes, Mendelsohn, Edmondson and Axel, 1996). The outcome is that the olfactory information imbibed at the site of the olfactory epithelium is translated topographically onto glomeruli at particular zones of the olfactory bulb. A further complication is that individual olfactory sensory neurons despite expressing only the one odorant receptor gene can respond to several odorants, and a given odorant can activate neurons with various odorant specificity (Firestein, Picco and Menini, 1993).

Besides processing convergent olfactory input from a multitude of olfactory sensory neurons, the olfactory bulb and cortex also exhibit a theta band oscillation or rhythm, which is coordinated with the natural breathing cycle even in the absence of odours (Fontanini, Spano and Bower, 2003). This demonstrates that the olfactory bulb also acquires information regarding airflow, thus is involved in regulating the process of monitoring sniffing which is essential for olfactory perception as it affects odorant concentration and Identification (Mainland and Sobel, 2006).

The olfactory bulb also comprises a master circadian pacemaker. This enhances olfactory responsivity, which oscillates in phase with wakefulness (odour-evoked event-related potentials are largest at 4:00 pm (Nordin, Lotsch, Murphy, Hummel and Kobal, 2003), drives rhythms in the piriform cortex and has projections to the suprachiasmatic nucleus of the hypothalamus, which regulates a plethora of circadian behaviours (Krout, Kawano, Mettenleiter and Loewy, 2002).

Primary olfactory cortex.

The olfactory bulb directly projects information via the lateral olfactory tract, which is composed of mitral cell and tufted cell axons to structures which are collectively known as the primary olfactory cortex (Shepherd, 2005). These structures include the amygdala, the piriform cortex, the entorhinal cortex and the frontal cortex. The primary olfactory cortex has bidirectional functionality between peripheral and analytic stages of sensory information processing and higher order brain structures, which initiate and sustain odour directed behaviour. It also receives input from neocortical and limbic areas, which express multisensory state dependent and information recall. For example, the hippocampus has afferent fibers along its entire length, which derive from the entorhinal cortex. The primary olfactory cortex also deciphers odour intensity, quality, familiarity and meaning and is considered to screen and modulate information based on experience and current behaviour (Wilson, Kadohisa and Fletcher, 2006).

Specifically the primary olfactory cortex is comprised of the: entorhinal cortex, periamygdaloid cortex, cortical amygdaloid nucleus, piriform cortex, olfactory tubercle, tenia tecta and anterior olfactory nucleus, all of which are highly interconnected although there is some regional variability. Of these only the piriform cortex has been well researched while there has been only sparse research in the other areas and their specific functions remain largely unknown (McNamara, Cleland and Linster, 2004).

The entorhinal cortex, which is located in the ventromedial surface of the temporal lobe, is an integral component of the hippocampal formation. Its structure gradually merges from the parasubiculum, presubiculum and subiculum into the CA1 of Ammon's horn of the hippocampus. It pre-processes data entering the hippocampus thus is comprehensively involved in learning and memory. Significantly, this is the reason for olfaction having such prominent access to the hippocampus thus provoking evocative memories (Gottfried, Deichmann, Winston and Dolan, 2002).

The periamygdaloid cortex and cortical amygdaloid nucleus receive direct input from the olfactory bulb and other primary and secondary olfactory areas and are central for emotional and behavioural responses to the intensity of significant pleasant or unpleasant odours (Doty, 2009). Other studies have also noted that the intensity of odours is also associated with activity in the piriform cortex (Rolls, Kringelbach and de Araujo, 2003) as well as the amygdala (Anderson, Christoff, Stappen, Panitz, Ghahremani, Glover, Gabrieli and Sobel, 2003). The amygdala connects the sensory and limbic areas of the cerebral cortex and subcortical brain regions essential for emotional and motivational responses (McDonald, 1998).

The piriform cortex, sometimes called the primary olfactory cortex, is the largest subdivision of the olfactory cortex and the principal centre before transduction of olfactory information to the higher system via the endopiriform nucleus (Suzuki and Bekkers, 2007). It has a relatively simple anatomy of a strongly laminated cortex with three main layers. The piriform cortex receives input from the entorhinal cortex and anterior olfactory nucleus, but most comes from the monosynaptic input of the olfactory bulb. This association pathway is quite plastic and it is considered that this area is cortically organised to code odours, which serves to identify familiar odorants. This also facilitates subsequent discrimination, quality and recognition (Wilson and Stevenson, 2003) as well as the learning and memory of odours and synchronising information between olfaction, vision, and taste (Gottfried, Deichmann, Winston and Dolan, 2002). It should be noted that odour coding is distributed throughout the olfactory cortex and not confined to just a single area (Franks and Isaacson, 2006). Information is then projected directly to the OFC, insula and dorsomedial nucleus of thalamus. From there it is integrated with multimodal and emotional cues and analysed to be projected back to the olfactory bulb, thus modulating cortical afferent activity (Sugai, Yoshimura and Onoda, 2005).

The olfactory tubercle is at the base of the cerebral hemisphere and receives direct projections from the olfactory bulb. It then projects to the hypothalamus and dorsomedial nucleus of the thalamus. It is an area which has not been widely studied but is believed to be involved in reward mechanisms (Carriero, Uva, Gnatkovsky and de Curtis, 2009).

The tenia tecta is a thin layer of gray matter on the dorsal surface of the corpus callosum in which the medial and lateral longitudinal stria are embedded. It receives information from the olfactory bulb and projects back to the other primary olfactory areas as well as to the olfactory bulb (Adamek, Shipley and Sanders, 1984). It has been suggested by Haberly (2001) that the tenia tecta has a role in retrograde memory recall, in the discrimination and learning of odour stimuli, and in the establishment of odour specific appropriate behavioural responses.

The anterior olfactory nucleus (AON) is a complex and significant structure which influences ongoing activity in many other olfactory regions, but its contribution to olfactory information processing is little understood (Brunjes, Illig and Meyer, 2005). Functionally it is considered that the anterior olfactory nucleus is involved in the inter hemispheric processing of olfactory information. The axons of the pyramidal cells of the AON project to the contralateral olfactory bulb and contralateral anterior olfactory nucleus via the anterior commissure. It also has distinct back projections to the olfactory bulb and distinct projections to and from the piriform cortex and from contralateral olfactory areas. Thus, it has a significant role in the organisation of neural input to both sides of the brain (Brunjes, Illig and Meyer, 2005).

Haberly (2001) considers the AON to perform like a unimodal feature detector, by receiving and assembling correlations between olfactory information and then projecting it to the proximal dendrites of the piriform cortex and other olfactory areas.

Secondary olfactory cortex.

Primary olfactory cortex projections synapse onto structures known as secondary olfactory areas. These areas are the hippocampus, dorsomedial nucleus of the thalamus, hypothalamus, OFC, the basal forebrain, and the limbic system including the insula, all of which are involved in motivated behaviour, autonomic reflexes and hormonal modulation. Despite the olfactory system being anomalous in comparison to the other senses in that it has direct projections to cortical regions without synapsing in the thalamus, projections between the primary olfactory cortex and secondary olfactory cortex i.e., OFC, do occur via direct cortico-cortical projections from prorhinal cortex to the posterolateral orbitofrontal region as well as the dorsomedial nucleus of thalamus (Doty, 2009). It is considered that the purpose of the thalamic connection is to provide a mechanism for conscious odour perception. As the amygdala and entorhinal cortex are part of the limbic system they provide the emotional and behavioural components of olfaction. Thus, this part of the brain is directly connected to the limbic system where structures for emotion are located.

The main structures in the limbic system which interact directly with the olfactory system are the amygdala and the hippocampus. As a result, only two synapses divide the olfactory bulb from the amygdala, which is central to the experience and manifestation of emotion (Shepherd, 2005). This is the reason why people have an immediate emotional response to certain pungent smells even before they have identified the odour. This experience has been replicated in examinations of cerebral blood flow, which have demonstrated a significant increase in flow to the amygdala with the presentation of a highly aversive odour. This was also associated with an aversive response. When comparing emotionally valenced stimuli, only olfactory stimuli in contrast to auditory and visual stimuli induced bilateral regional cerebral blood flow increases in the amygdala (Royet, Zald, Versace, Costes, Lavenne, Koenig and Gervais, 2000).

Three synapses separate the olfactory bulbs from the hippocampus, which is the essential structure for associative learning and various forms of memory. Thus, the olfactory system, due to its close proximity and direct neural projections to both the amygdala and the hippocampus, has a disproportionate accessibility to these structures in comparison to the other senses. This direct neuroanatomical link between emotion, memory and olfaction is the reason for the “Proustian Memory” where a smell from the distant past recreates more evocative and emotion laden memories (Herz and Schooler, 2002). These odour memories do not decay as quickly as memories from other sensory modalities due to their unique neuroanatomical position (Engen and Ross, 1973). This unique configuration is the reason for odours having such particularly potent memories and emotion. It is also the reason why emotion and odour are so readily associated.

Paradoxically the olfactory system is constructed so that prolonged exposure to disgusting odours results in habituation and an eventual barely noticeable background aroma. Studies using fMRI conducted by Sobel, Prabhakaran, Zhao, Desmond, Glover, Sullivan and Gabrieli (2000) indicate that a great deal of this habituation is occurring in the primary olfactory cortex and prevails despite the continual presence of the odour.

From the limbic system, olfactory information is projected to the OFC, which also receives inputs from other senses such as taste. Thus, it is the part of the brain which distinguishes flavour. From the OFC, olfactory information is relayed to the neocortex for cognitive processing.

The Orbitofrontal Cortex (OFC)

Introduction

The OFC is one of the least understood areas of the prefrontal cortex and many of its functions remain obscure. However, it is known to be a neurological intersection for sensory integration and adjustment to autonomic reactions. In addition, it is an area which

facilitates the learning, prediction and decision making of emotionally based and reward associated behaviour.

History

The frontal lobes were first implicated in the processing of emotion because of the traumatic brain injury to Phineas Gage in 1848. His frontal lobes were decimated when a metal tamping iron was blown through them. As a result, he exhibited profound personality and emotional changes without any other apparent change in intellect. After reconstruction of the site, the brain damage was considered to be in the OFC and anterior cingulate cortices (Damasio, Grabowski, Frank, Galaburda and Damasio, 1994). Subsequently researchers have been able to further elucidate the role of the OFC in social interaction, emotion, and decision making through brain imaging and work with human patients and animals who have suffered neurological damage in similar locations as that by Gage (Bechara, Damasio and Damasio, 2000).

Difficulties due to OFC damage include poor decision making, lack of affect, social inappropriateness and irresponsibility. There is also impairment in identifying social signals that are important for decision making such as face and voice expression (Hornak, Bramham, Rolls, Morris, O'Doherty, Bullock and Polkey, 2003).

Anatomy

The OFC forms an important subdivision of the prefrontal cortex. However due to substantial variability in gyral and sulcal patterns across individuals it has been difficult to obtain accurate and reliable OFC measurements. Also because of its relatively unapproachable location, it has been notably less explored than other prefrontal sectors, notably the lateral prefrontal cortex (Cavada and Schultz, 2000).

The prefrontal cortex may-be divided into three main sections based on the divisions of the mediodorsal nucleus (Fuster, 2001). The medial part of the mediodorsal nucleus projects to the orbital surface of the prefrontal cortex and it is this area, which is

called the OFC. It is the most ventral portion (rests on the upper wall of the orbit) of the prefrontal cortex and has prolific connections to the amygdala and dorsomedial thalamus (Zald and Kim, 1996). For clarification, Walker (1940) divided this region into five different areas numbered 10, 11, 12, 13 and 14. It is primarily involved in emotion and receives input from visual, taste, olfaction and touch systems.

Connections

The OFC receives inputs from the five sensory modalities, which include gustatory, olfactory, somatosensory, auditory and visual (Carmichael and Price, 1995). However it is to be noted that it is the secondary taste and olfactory cortex due to it receiving major neuroanatomical projections from the primary taste cortex and primary olfactory cortex (piriform cortex) (Baylis, Rolls and Baylis, 1995). Input from other areas which include: visceral inputs from the thalamus (Carmichael and Price, 1995); direct visual input from the inferior temporal cortex (Barbas, 1995); and inputs from both auditory and somatosensory cortical areas. Because the OFC is neuroanatomically unique in that it receives input from more than one sensory modality, it is known as a heteromodal region. Unimodal regions of the cortex receive inputs from only one sensory modality and this includes vision, audition, and somatosensation, which are heavily interconnected to heteromodal regions of the neocortex. Consequently, this is likely to make the OFC the most polymodal region in the cortical mantle (Barbas, 1995).

The OFC also has strong direct reciprocal connections with the amygdala, thalamus, cingulate cortex, temporal lobe and entorhinal cortex (Insausti, Amaral and Cowan, 1987). Input from the hippocampus is via the subiculum (Cavada, Company, Tejedor, Cruz – Rizzolo and Reinoso - Suarez, 2000). Secondary reinforcers such as money also activate the OFC as neuroimaging studies confirm (O'Doherty, Kringelbach, Rolls, Hornak and Andrews, 2001).

As the OFC has such widespread neural connectivity it has enormous capacity to assimilate sensory and visceral motor input thus regulating behaviour through both visceral and motor systems. This leads to the conclusion that the OFC is an integral neural component in emotional processing (Bechara, Damasio and Damasio, 2000). Due to its direct connections with the amygdala it also means that together these two brain areas are likely to play a considerable role in goal directed behaviour.

Consequence of Lesions

Damage to the OFC of monkeys causes impairment to learning paradigms, which involve reward, especially when reward contingencies have been modified or changed. For instance, monkeys with OFC lesions may keep responding to former reward paradigms which are no longer appropriate; specifically by continuing to respond to non rewarded contingencies and nonresponding to new reward contingencies. Iversen and Mishkin (1970) noted that monkeys with OFC damage were also impaired on Go/No go trials as they would Go on the No go trial. Other similar experiments have demonstrated outcomes where monkeys would continue to respond to formerly rewarded tasks in object reversal tasks and conversely in extinction paradigms, keep responding to a non rewarded object (Murray and Izquierdo, 2007).

Rosenkilde (1979) found that lesions to different areas of the OFC are a feature of reversal and extinction paradigms. For instance, damage to the caudal OFC induces the extinction response to increase and damage to the inferior convexity of the OFC is implicated in Go/No go differentiation. Other OFC lesions cause an inhibition of sensory specific satiation (Murray and Izquierdo, 2007). Lesions to the caudal region of the OFC also cause changes to the expression of emotional behaviour in rhesus monkeys. For instance, they exhibit blunted emotional responses to fake snakes and display more mild aggression to human intruders (Izquierdo, Suda and Murray, 2005). They also do not rank

food in order of preference in the same manner as they did pre-lesion (Baylis and Gaffan, 1991).

Much of the current knowledge of the function of the OFC in humans has come from studies of patients and animals with lesions centered in this region. Amongst humans, lesions of the OFC may induce euphoria, impulsiveness, lack of affect, impaired memory about learning (including positive and negative reinforcement), impairment on short term memory for objects and irresponsibility (Bramham, Morris, Hornak, Bullock and Polkey, 2009). It is thought that this may in part be due to a failure to accommodate the new reinforcement contingencies once these contingencies have been changed (Rolls, 2005). This is also the likely explanation for poor performance on the Iowa Gambling task noted amongst those with ventromedial prefrontal cortex damage (Maia and McClelland, 2004). Lesions which are more lateral to the OFC have a marked effect on delayed matching to sample and delayed matching to nonsample tasks where objects have to be remembered for short periods (Kowalska, Bachevalier and Mishkin, 1991). It is thought that neurons in this location assist the short term memory of the visual object by maintaining the representation during the delay period (Rao, Rainer and Miller, 1997).

Other noticeable changes to behaviour in those with OFC lesions include a failure to report regret or anticipate possible negative consequences of choice. They also demonstrate reduced social perception such as the ability to accurately perceive emotional facial expressions and other information about faces. This may indicate that face and voice expression identification is impaired. Anderson, Barrash, Bechara and Tranel (2006) noted that early onset damage of the OFC does not recover over time and may lead to deficits in decision making and impulsivity, which has implications for behaviour and addictions. However although the OFC is critical in decision making other cortical components such as the amygdala, the somatosensory insular cortices and peripheral nervous system are also involved.

Prediction of Reward Value

Good decision making is based on one's ability to accurately predict an outcome (Schultz and Dickinson, 2000). Researchers investigating such matters using neuroimaging have often applied classical conditioning techniques, where a previous neutral stimulus is paired with reward or punishment. For instance, a fMRI study conducted by Gottfried, O'Doherty and Dolan (2003) presented subjects with predictive cues combined with food-related odours. They contrasted neural activity to the cues before and after devaluation (feeding to satiety) of the associated food. The results indicated that neurons in the OFC monitor the relative changes in the predictive reward values of the odours. This indicated that the OFC is responsive to reward value rather than sensory features.

Subsequent authors of fMRI studies have concluded that the reward related brain structures are the OFC, amygdala, ventral striatum and medial prefrontal cortex and that the orbital frontal cortex is specifically involved in immediate reward prediction. Secondary rewards and punishers are also represented, for instance the winning and losing of money. Thus, one of the major functions of the OFC is rapid stimulus reinforcement association learning (Tanaka, Doya, Okada, Ueda, Okamoto and Yamawaki, 2004). This learning includes visual, olfactory, taste or touch stimuli. Rolls (2004) notes that the OFC not only performs rapid reverse stimulus reinforcement associations but also performs this role more efficiently and rapidly than the amygdala. Other associations include threat. For instance, MRI scans were used to monitor the activation of brain regions when participants were presented with unambiguous threat (angry faces). Results showed that females activated the OFC and amygdala; however, males showed less activation of these regions (McClure, Monk, Nelson, Zarahn, Leibenluft, Bilder, Charney, Ernst and Pine, 2004).

Further neuroimaging studies have elucidated the function of the medial OFC in the evaluating and discrimination of reward value, which has no immediate behavioural

consequence. For instance the evaluation of the affective properties of gustation, (Small, Gregory, Mak, Gitelman, Mesulam and Parrish, 2003), touch (Rolls, O'Doherty, Kringelbach, Francis, Bowtell and McGlone, 2003), olfaction (Rolls, Kringelbach and de Araujo, 2003), and flavour which simultaneously incorporates both taste and smell (De Araujo, Rolls, Kringelbach, McGlone and Phillips, 2003).

Other studies such as the Positron Emission Tomography investigation by Schnider, Treyer and Buck (2005) also found that the medial OFC monitors outcomes even when no reward is at stake. Thus the OFC is deemed to be involved in hedonic and reinforcement processing, however it appears that there is considerable overlap within the region. An fMRI study has attempted to differentiate these areas (Murray, O'Doherty and Schoenebaum, 2007) and several distinctions have been noted. Firstly, it is believed that the medial regions of the OFC are more likely to be associated with positive reinforcement independent of behavioural significance suggesting primarily a hedonic response in this region. The lateral regions of the OFC were more likely to be associated with negative reinforcement confirming the evaluation of negative stimuli in these regions (Elliott, Agnew and Deakin, 2010).

Reward

Much of the input into the OFC comes via the posterior section where it is assimilated with input from other senses. As it is a multimodal receiving centre, stimuli become encoded with a reward value representing incentive, pleasantness and need (Kringelbach, 2005). For instance, Kringelbach, O'Doherty, Rolls and Andrews (2003) conducted a study of activity in the OFC, which demonstrated a sensory-specific diminution in the value of a food eaten to satiety but not to other food. This was demonstrated by using fMRI technology whilst feeding people to 'sensory specific satiety.' Hungry participants were scanned and presented with two foods one of which was eaten to satiety. The food eaten had a marked decrease in reward value, however while still

satiated, the other food did not lose its reward value. Thus, there is a decrease in OFC neuronal activation when a specific food is eaten to satiation and participants also report a concomitant loss of pleasantness. The scans indicated that it is the anterior section of the OFC, which monitors change in the reward value of foods eaten. Similar results were obtained for olfaction (O'Doherty, Rolls, Francis, Bowtell, McGlone, Kobal, Renner and Ahne, 2000).

Thus, the results of many studies demonstrate that the reward value of the senses of taste, olfaction and somatosensory components to food are expressed in the OFC. The study of food and its concomitant pleasant and or aversive sensations is an interesting exercise given that food is required for life and has greater hedonic value when one is hungry (Kringelbach, 2005). Caloric intake is also found to be regulated by hedonic value and by homeostasis (Saper, Chou and Elmquist, 2002). This is a very complex process involving cortical and subcortical neuronal regions where previous learned experience, memory, conditioning, planning and prediction play a significant role. This is especially pertinent given a person's previous sensory experience with a food, particularly pleasure and other variables such as temperature, salt and fat content, viscosity, identity, intensity and expectation.

Correlations of pleasantness in the brain with one of the senses are almost exclusively to be found in the medial OFC. However, correlations with pleasantness and OFC activity are not just limited to food. It also includes pleasantness for taste (De Araujo, Kringelbach, Rolls and McGlone, 2003); odour (Rolls, Kringelbach and De Araujo, 2003; Katata, Sakai, Doi, Kawamitsu, Fujii, Sugimura and Nibu, 2009); food texture and fat content (De Araujo and Rolls, 2004); oral temperature (Craig, Chen, Bandy and Reiman, 2000); IV drug related rush (Völlm, de Araujo, Cowen, Rolls, Kringelbach, Smith, Jeppard, Heal and Matthews, 2004); irritating sound (Blood, Zatorre, Bermudez and Evans, 1999) and profoundly pleasurable sound (Blood and Zatorre, 2001).

Other single neuron studies of primates demonstrate that the OFC is the location of the reward value of sight as it receives significant visual input from the temporal lobe. Neurons encode the reward and non reward associations of visual, smell and taste of food and even adjustments to the relative reward value. Thus, it has been concluded that the OFC has a significant role to play in emotion and motivation, and related subjective states.

Response Inhibition

Another important function of the OFC includes response inhibition (Elliott, Dolan and Frith, 2000). Research has elucidated that participants who previously learned behaviours which had been rewarded but are now no longer rewarded exhibit perseveration in reverse learning tasks (Dias, Robbins and Roberts, 1996). However, it seems that this behaviour may be due to a failure to learn to respond to the current reward paradigm. Monkeys and patients with lesions to the lateral OFC demonstrate severe impairment on the reversal aspect of an object reversal learning task, which cannot simply be explained as a perseverative response (Hornak, O'Doherty, Bramham, Rolls, Morris, Bullock and Polkey, 2004).

Taste

There are major and significant cortical representations of taste in the OFC. This includes all types of taste, sweetness, bitterness, sourness and saltiness (Rolls, Yaxley and Sienkiewicz, 1990). As taste is a primary reinforcer, it therefore has an important role in learning paradigms where neutral stimuli are paired with taste. However, a profoundly important observation is that taste neurons in the orbitofrontal region stop responding once satiety is reached as they are modulated by hunger. As the reward value of the taste is represented in the OFC it means that not only is the appeal of a taste blunted once appetite is satiated but taste neurons begin to slow and then cease their firing rate as the individual reaches satiety (Rolls, Critchley, Wakeman and Mason, 1996). Interestingly many taste neurons are sensory specific and only respond to particular foods, which means that taste

neurons for other foods can still maintain high firing rates. This particular occurrence is not limited to just taste olfaction or flavour. It also occurs in respect to thirst. Select OFC neurons fire immediately to the taste of water when one is thirsty but when thirst is slaked cease to respond (Rolls, Yaxley and Sienkiewicz, 1990). The pleasantness of the taste of water is also represented here (De Araujo, Kringelbach, Rolls and McGlone, 2003). Thus, the OFC is profoundly attuned and responsive to the various senses and processes the value of rewarding outcomes of voluntary behaviour (Tremblay and Schultz, 1999). This indicates that the OFC is crucially involved in the reward value of various behaviours.

Although the words taste and flavour are often used interchangeably, this is not entirely accurate. There are only five distinct taste sensations which the tongue can differentiate and hundreds of scents which the nose can distinguish. Flavour is a combination of both taste and smell and it is estimated that at least 75% of what we perceive as taste is comprised of smell. Given that the OFC receives direct major projections from both olfactory and gustatory cortices, one would anticipate that it is likely to be an area where flavour is cortically represented. As predicted, this is in fact exactly the case. The OFC is the area where flavour is located because it is an area of neuronal convergence. Specifically in humans this convergence of taste and smell stimuli is located in the lateral anterior aspect of the OFC. Correlations for the evaluation of smell, and for pleasantness, were located in the medial anterior aspect of the OFC (De Araujo, Rolls, Kringelbach, McGlone and Phillips, 2003). Rolls and Baylis (1994) noted that amongst the unimodal regions of taste and smell, 13% of individual neurons demonstrated convergence thus responding to both taste and odour to create flavour.

Other unimodal regions of the OFC also included single neurons which demonstrated convergence. These included taste and visual inputs and olfactory and visual inputs (Rolls and Baylis, 1994). They noted that many of these multimodal neurons were

frequently located close to unimodal tracks into that region. This suggests that multimodal inputs are being derived from unimodal inputs. This finding is consistent with other research, which has demonstrated the OFC as shaping the reward value of primary and secondary reinforcers. Other neurons in the OFC are activated by the texture of food in the mouth, temperature, viscosity and fat content but are still correlated to ratings of pleasantness (Kringelbach and Rolls, 2004).

Olfaction

As has been previously noted, the OFC has a major role in olfactory processing which has been demonstrated in numerous human neuroimaging studies and single neuron studies in primates. A study using pyridine, menthone and amyl acetate as olfactory stimuli, measured brain activation using fMRI. The results of this study indicated that brain activation occurred in the OFC, the entorhinal cortex and cingulate (Levy, Henkin, Hutter, Lin, Martins and Schellinger, 1997). The region in the OFC, which is activated by odours, can be divided into two functional areas. The first is activated by odour alone and the second is activated by odour and taste. In primates, the area activated by odour alone occupies 65% whilst 35% of the area is to both odour and taste (Critchley and Rolls, 1996).

The OFC is also involved in the processing of the judgment of hedonic value of odours, odour memory, Odour Identification and Odour Discrimination, (Zald and Pardo, 2000). Gottfried, Deichmann, Winston and Dolan (2002) found in their study that the caudal OFC is associated with odour detection, where-as the more rostral regions were involved in working memory, associative learning and odour recognition memory.

Other studies which specifically examined the hedonicity of an odour, i.e., pleasant / unpleasant, found that different regions of the OFC were activated. Pleasant odours activated the medial OFC and ventromedial prefrontal cortex, while unpleasant odours activated the lateral OFC and neighbouring inferior prefrontal cortex (Gottfried, O'Doherty and Dolan, 2003). This medial / lateral responsiveness divide to pleasant and unpleasant

stimuli also applies to the other senses, indicating that these regions are important for general sensory hedonic processing. Interestingly there is a sensory specific marked reduction in the activation of the human OFC to the odour of banana when the banana is eaten to satiation (O'Doherty, et al, 2000). A similar study replicated these results. Kringelbach, O'Doherty, Rolls and Andrews (2003) noted that when a liquid food was eaten to satiation, there was a significant decrease in the activation of the OFC and a subjective decrease in the pleasantness.

The medial / lateral divide dividing pleasant and unpleasant olfactory stimuli is not straight forward when it comes to hedonically complex odour mixtures. When presented with a complex mixture the medial OFC which responds to pleasant odours minimizes unpleasant constituents and emphasizes the pleasant. Conversely, in the cortex, which represents the unpleasant odours, the unpleasant was emphasised and pleasant minimized. Thus, pleasant odours can be a combination of pleasant and unpleasant odours which the brain simultaneously separates and represents. This can create an interesting phenomenon where an unpleasant odour when mixed with other pleasant odours forms a combination and synergy whereby the resultant odour is enhanced (Grabenhorst, Rolls, Margot, da Silva and Velazco, 2007). For instance, nonhuman mammalian pheromones are commonly used as perfumery ingredients and contribute to the overall scent of the perfume (Berliner, Jennings-White and Lavker, 1991). An example of this is civetone, a pheromone that is sourced from the glands of the African civet cat. At extremely low dilutions it is very pleasant and used in perfumes, which without it would not be as attractive.

To date, it has been hypothesised that emotion can be reduced to dimensions of arousal and hedonicity (Lang, 1995) and that hedonic experience is represented in the OFC. Research conducted by Anderson, Christoff, Stappen Panitz, Ghahremani, Glover, Gabrieli and Sobel (2003) reported that the amygdala is activated by intensity / arousal but not valence / hedonicity which was the sole domain of the OFC. Other fMRI research by

Winston, Gottfried, Kilner and Dolan (2005) indicated that when hedonicity was held constant, the amygdala activated to odour intensity for both pleasant and unpleasant odours but not neutral odours. However, conversely when they held intensity constant at high concentrations the amygdala was activated by both pleasant and unpleasant odours but not neutrally valenced odours. This outcome indicates that the amygdala is activated by an odour intensity / odour hedonicity interaction, which is far more complex than previously considered. Thus, the amygdala is activated by intense odours, which are emotionally salient (pleasant or unpleasant). This has survival value in that intense neutral odours are unlikely to be either threatening or life promoting.

Summary

The OFC is the location where the sensory integration and emotional processing of hedonic experience occurs. The posterior aspect of the OFC integrates sensory information for continuing multimodal integration. The anterior aspect of the OFC is where stimuli are apporportioned hedonicity or reward value, which is modulated by hunger and other internal states, which can influence further behaviour. Further input is monitored and reward and hedonicity learned and stored for future reference. Thus, there is a continual reciprocal stream of information being exchanged between various regions of the OFC, amygdala anterior cingulate and brain regions.

Ramifications

The OFC is engaged in reciprocal sensory inputs from a variety of cortical and subcortical structures and is also involved in reward and reinforcement. Thus damage to OFC is demonstrated by a plethora of difficulties including impaired behavioural and personality change, impaired reward contingencies and also impairment in the learning and reversal of reward associations. Response inhibition is particularly sensitive to OFC dysfunction. This has ramifications for those with PTSD.

The OFC is selectively activated during the encoding of both visual and auditory information. Thus, it is considered that the OFC may exert a top down regulation of other regions of the brain including the medial temporal and lateral frontal cortex, which may enable the further regulation of information, and processing new information (Frey, Kostopoulos and Petrides, 2004). As it can receive and influence information about the emotional and basic biological significance of stimuli, the OFC is the principal site for subjective emotional processing in the brain. This is because the OFC has executive function and regulating behaviour based on emotional input and reinforcement. Therefore, as anosmia and poor smell Identification are common indicators of OFC dysfunction, olfactory dysfunction may predict behavioural and emotional decompensation. This may explain why those veterans with PTSD have poor Olfactory Identification in comparison to veterans without PTSD.

Olfactory Dysfunction

Olfactory disorders are much more prevalent in the population than has previously been recognised. For instance in the Landis, Konnerth and Hummel (2004) study, decreased olfactory function was found to be at 16% and anosmia at 5%. There are a plethora of reasons for diminished olfaction with approximately 60% being explained by damage to the olfactory neuroepithelium (Deems, Doty, Settle, Moore-Gillon, Shaman, Mester, Kimmelman, Brightman and Snow, 1991) head trauma, nasal polyposis, inflammatory diseases of the nose / paranasal sinuses, respiratory dysfunction and post respiratory tract infection (Damm, Temmel, Welge-Lussen, Eckel, Kreft, Klussmann, Gudziol, Huttenbrink and Hummel, 2004).

Structural MRI studies, which have been used to examine the olfactory bulbs, have found that olfactory bulb volume is decreased in those with olfactory loss due to both infection and trauma. This decrease in volume is related to duration of disease and parosmia (incorrectly perceived sense of smell) (Mueller, Rodewald, Reden, Gerber, von

Kummer and Hummel, 2005). Although olfactory bulb volume is diminished in those with olfactory loss due to nasal polyps and infection, it is significantly less diminished than those with a head injury. It is hypothesised that this is due to neural regeneration being more viable in those with loss due to infection rather than trauma where shearing and scarring is an issue (Rombaux, Weitz, Mouraux, Nicolas, Bertrand, Duprez and Hummel, 2006).

Olfactory dysfunction is not limited to disorders related to peripheral issues and the olfactory bulb, but is also present in other mental and neurological (central) disorders. This includes but is not limited to PTSD. The mechanism of the relationship between olfactory dysfunction and these disorders is not yet clearly understood. For example olfactory identification, threshold and discrimination are differentially affected by various disorders or conditions. These patterns of olfactory functioning, which are referred to as, ‘olfactory signatures,’ may contribute to our understanding of the olfactory system and the presence of olfactory dysfunction in PTSD. Furthermore, it is important to understand how comorbidity (e.g. depression) may influence olfactory functioning in those with PTSD.

The findings regarding variable relationships between peripheral factors, central disorders and olfaction are detailed below. This is especially pertinent considering the overlap between the olfactory system and the limbic system given the limbic system is central to PTSD.

Olfactory Dysfunction and the Limbic System: Implications

The sense of smell is unique and differs subtly and profoundly from the other senses. It is bilateral, is not mediated by the thalamus, involves substantial neurogenesis and has direct links to the amygdala. It is the only sensory modality which has this direct access to the amygdala. As a result, odours have the capacity to elicit immediate and strong emotional memories, much greater than the other senses. Thus all of the processes

of olfaction even odour perception involve the limbic system. This early involvement of the limbic system is not matched by the other sensory modalities. The fact that olfactory pathways access the very same anatomical pathways implicated in memory and emotion is a profound distinction.

The amygdala is preferentially occupied with the long term accommodation of explicit memory for emotionally salient events. For instance, it has been noted that the amygdala was activated amongst those with PTSD when they recall the traumatic incident which caused the disorder (Rauch, van der Kolk, Fislcr, Alpert, Orr, Savage, Fischman, Jenike and Pitman, 1996).

As the olfactory system shares a common neural pathway with much of the cognitive and emotion processes that are abnormal in many of the neurodegenerative and psychiatric disorders means that these disorders may-be accompanied by dysfunction of olfactory processing. As a result, in recent years there have been a number of studies investigating olfactory function in various neuropsychiatric disorders. Dysfunctions in emotional processing areas are consequently expected to affect olfactory perception also.

Alternatively, olfactory probes may provide additional measures of some neuropsychiatric symptoms. For instance, the neural treatment and organisation of olfactory data is shared by the same limbic neuroanatomical structures (ventromedial temporal lobe, basal forebrain, prefrontal cortex, and diencephalon) that have been implicated in the pathology of schizophrenia (Turetsky, Hahn, Arnold and Moberg, 2009). This is both in terms of anatomy, neurochemistry, and neurodevelopmental time course. As there are only two synapses between olfactory receptors and secondary cortical and subcortical areas the olfactory system provides for direct access to neurological areas implicated in schizophrenia. Studies of olfaction of those with schizophrenia have demonstrated impairments in Threshold sensitivity, Olfactory Identification and odour recognition. However, the most salient feature about the convergence of neural pathways

for schizophrenia and olfaction is that olfactory decline is one of the first symptoms of the disorder and is correlated with the progression of the disease (Fusari and Molina, 2009). Not only is this a feature of schizophrenia but other neurodegenerative disorders.

Other neurodegenerative disorders where olfactory deficits are cardinal features and precede the disorders include Alzheimer's disease, multiple sclerosis, and Parkinson's disease (Hawkes, 2006). Other developmental disorders and psychiatric disorders where olfaction is a prominent feature are described below in this document.

In summary, it appears that neurodegenerative disorders, developmental disorders and psychiatric disorders have olfactory deficits with some having a specific pattern. Indeed some disorders may have a specific signature of olfactory dysfunction related to precise neurobiological alterations and disease progression.

Other reasons for olfactory dysfunction include age, smoking, gender, intracranial tumours or lesions, epilepsy, toxic exposure, renal disease, leprosy (Mishra, Saito, Barbash, Mishra and Doty, 2006). The more common reasons for this dysfunction are briefly considered below with the causes being arbitrarily divided into peripheral and central, although there is often considerable overlap. Peripheral reasons are external to the brain and usually involve nasal disease, whilst central reasons comprise brain dysfunction. The central reasons for dysfunction will then be further divided into the categories of developmental disorder, neurodegenerative and psychiatric disorders with PTSD then becoming the focus of this investigation.

Olfactory Dysfunction: Peripheral Reasons

Age

The most common reason for olfactory decline is the accumulation of age related changes. These include the development of neurodegenerative disorders, ossification of the foramina in the cribriform plate and resultant incremental damage of the epithelium due to viral insult. Impairment rates are as high as 25% in those who are 50 years old or

older (Bramerson, Johansson, Ek, Nordin and Bende, 2004) and amongst those 80 years of age and older it is as high as 75% (Doty, Shaman and Dann, 1984).

Viral

Of these reasons for olfactory dysfunction viral infections are the most common for enduring hyposmia or anosmia (Deem, Doty, Settle, et al 1991) (refer to Appendix D for definitions). Clinical olfactory disorders have been associated with recently experienced respiratory viral infections (Welge - Lussen and Wolfensberger, 2006) and it is considered highly likely after observing animal models that general respiratory viruses may influence neurodegenerative processes (Majde, 2010).

Toxic Chemicals

Chemical exposure is estimated to account for approximately 1 – 5% of all olfactory disorders (Smith, Davidson and Murphy, 2009) and some of this loss can even occur after brief exposure. Some of the offending compounds include dust exposure; manufacturing processes such as varnishes and ammonia; organic compounds such as acetone and cement; metals such as cadmium and chromium; and airborne toxins such as herbicides and pesticides. Chronic exposure exacerbates the problem considerably (Doty and Hastings, 2001).

Animal studies have demonstrated that olfactory receptor neurons not only absorb but transport heavy metals such as gold, cadmium, zinc (Persson, Henriksson, Tallkvist, Rouleau and Tjälve, 2003) and manganese to the olfactory bulb at a rate of 2.5 to 3mm per hour (Elder, Gelein, Silva, Feikert, Opanashuk, Carter, Potter, Maynard, Ito, Finkelstein and Oberdörster, 2006). It is considered highly likely by Doty (2008) that some air borne toxins are implicated in the aetiology of several neurodegenerative disorders such as Parkinson's and Alzheimer's disease.

Olfactory Dysfunction: Central Reasons

Developmental Disorder

ADHD.

The essential features of ADHD are enduring hyperactivity / impulsivity and inattention, which occur significantly more often than in other individuals at a similar level of maturity. According to the *DSM-IV-TR* symptoms must have been evident before age 7 (American Psychiatric Association, 2000). Longitudinal studies suggest that approximately 80% of those diagnosed in childhood will meet the clinical criteria for ADHD in adolescence and 67% will have symptoms persisting into adulthood (Fischer, 1997). Although the salient feature of ADHD is inattention, a host of other cognitive deficits may also be exhibited. For instance, difficulties with planning, problem solving, sustaining goal directed behaviour and working memory. These deficits are indicative of poor executive functioning, which is considered to be due to dysregulation of the frontal lobes (Gansler, Fucetola, Kregel, Stetson, Zimering and Makary, 1998).

Although there are very few studies to date examining ADHD and olfaction, studies which have extensively measured executive functioning and included an odour Identification test have noted olfactory impairment in those with ADHD (Murphy, Barkley and Bush, 2001); (Gansler, Fucetola, Kregel, Stetson, Zimering and Makary, 1998). These Olfactory Identification deficits were attributed to prefrontal lobe dysfunction (Murphy, Barkley and Bush, 2001). However, a later study examining children and adolescents diagnosed with ADHD both with and without medication found improved odour sensitivity (Threshold) in children with untreated ADHD. Olfactory Discrimination and Identification remained unaffected. Medicated patients did not differ significantly from healthy control subjects (Romanos, Renner, Schecklmann, Hummel, Roos, von Mering, Pauli, Reichmann, Warnke and Gerlach, 2008).

Asperger's disorder.

Asperger's disorder is a pervasive developmental disorder very similar to autistic disorder in intelligent children. Those with Asperger's present with sustained severe social interaction and stereotyped restricted behaviours and interests. However, those with Asperger's differ from those with an autistic disorder in that they do not have any significant language delay or mutism and speak fluently by age 5 but with abnormalities in comprehension and pragmatics. Cognitive development and age appropriate self-help skills remain intact (Sadock and Sadock, 2003).

To date very few olfactory studies have been conducted assessing those with Asperger's disorder. However, a study by Suzuki, Critchley, Rowe, Howlin and Murphy (2003) measured Odour Threshold and Odour Identification in 12 males with Asperger's syndrome and 12 matched control subjects. Their results indicated that in comparison to control subjects, Asperger's syndrome subjects demonstrated significant Olfactory Identification impairment but comparable Odour Threshold scores. They concluded that as the OFC is implicated in Olfactory Identification deficits then it is also associated with the deficits in Asperger's syndrome.

Neurodegenerative

Alzheimer's.

Alzheimer's disease is a progressive neurological disorder marked by increasing cognitive decline. Symptoms frequently begin with an inability to incorporate new information (despite the ability to recall previously learned facts), an inability to recall words and an inability to orient to new environs. *DSM-IV-TR* diagnostic criteria include the development of multiple cognitive deficits including memory impairment and at least one other cognitive deficit from the following: language disturbance, apraxia, agnosia and disturbance in executive functioning (American Psychiatric Association, 2000). The general prevalence rate of dementia in all those aged 65 or more is 5% - 6%. However the

prevalence rate increases exponentially after age 65 as approximately 33% over the age of 85 have dementia. Of those with dementia, approximately 50% - 80% is of the Alzheimer's type (Ott, Breteler, van Harskamp, Claus, van der Cammen, Grobbee and Hofman, 1995). To date an unequivocal diagnosis of Alzheimer's disease can only be made by neurological examination at autopsy.

The earliest stages of cortical abnormality in those with Alzheimer's are thought to be relatively focal with the transentorhinal and then the entorhinal cortex mostly affected. These areas are a part of the olfactory cortex and involve memory, emotion and imparting sensory afferents to the hippocampus (Braak and Braak, 1998). It has been considered by Braak and Braak (1992) that lesions to these areas disengage the hippocampus from the isocortex thus preventing memory functioning. It has been postulated by Esiri and Chance (2006) that a reason for the vulnerability of the olfactory and association cortex is due to its considerable neural plasticity.

Currently there is a great deal of evidence demonstrating olfactory impairment in those with Alzheimer's disease. Both Olfactory Threshold and Identification are affected by Alzheimer's disease. Olfactory Identification deficits are the first to manifest and are often predictive of a future diagnosis of Alzheimer's disease as olfactory dysfunction is among the first signs of Alzheimer's disease (Tabert, Liu, Doty, Serby, Zamora, Pelton, Marder, Albers, Stern and Devanand, 2005).

The ability to accurately identify odours incorporates a considerable degree of cognitive load, as it requires perceptual processing, olfactory sensory functioning and semantic memory (Cain and Potts, 1996). Extensive difficulties with odour Identification have been consistently demonstrated in those with Alzheimer's disease (Peters, Hummel, Kratzsch, Lotsch, Skarke and Frolich, 2003; Moberg, Doty Mahr, Mesholam, Arnold, Turetsky and Gurr, 1997). However, studies also indicate that those with probable Alzheimer's (or at considerable risk of developing Alzheimer's) have difficulty identifying

odours. For instance Calhoun-Haney and Murphy (2005) tested subjects genetically predisposed to Alzheimer's who were apolipoprotein E positive and followed them up 4 years later. Their results showed that Olfactory Identification deficits occurred before other neurocognitive dementia screening test scores declined. This was considered to be due to early preclinical changes in olfactory cortices. Another study examining siblings of those with probable Alzheimer's disease found that the siblings demonstrated odour Identification deficits but those with the greatest deficits were those who were siblings and apolipoprotein E positive (Handley, Morrison, Miles and Bayer, 2006). An earlier study by Bacon, Bondi, Salmon and Murphy (1998) found changes in threshold deficits occurred the year immediately preceding a diagnosis of Alzheimer's disease.

Other studies have documented a relationship between Alzheimer's disease and anosmia (reduced odour sensitivity). They have noted an association between degree of severity and degree of anosmia (Meshulam, Moberg, Mahr and Doty, 1998) and with a rapid increase in dementia and a sudden decline in sensitivity (Nordin, Murphy, Nijjar and Quinonez, 1993). In the initial stages of Alzheimer's, odour sensitivity / threshold often remains intact but progressively deteriorates indicating that this is related to neurological deterioration rather than rhinological status.

Down Syndrome.

Down Syndrome is the most common congenital chromosome disorder and is characterised by mental and physical retardation, dysmorphic facial features, cardiac and other anomalies, and immune dysfunction.

Those with Down Syndrome have been shown to have Olfactory Identification deficits, which get progressively worse with increasing age (Warner, Peabody and Berger, 1988). Other olfactory deficits include threshold and recognition memory (Murphy and Jinich, 1996). McKeown, Doty, Perl, Frye, Simms and Mester (1996), demonstrated that adolescents with Down Syndrome have normal olfactory function but impairment in mid-

life is likely to be related to the neurodegenerative processes associated with Alzheimer's disease (Hemdal, Corwin and Oster, 1993). The entorhinal cortex, which is an olfactory processing area, shows the first signs of neuropathological changes in Alzheimer's disease. Risk factors for Alzheimer's include Down Syndrome and those who are apolipoprotein positive (ApoE). A study by Sliger, Lander and Murphy (2004), found that among Down Syndrome participants, those who were (ApoE) had poorer odour Identification than those without. This indicates that those with Down Syndrome who have an additional genetic risk factor for Alzheimer's disease via the (ApoE) have greater deficits in odour Identification.

Epilepsy.

Olfactory deficits are common in epilepsy with right side foci the most disruptive. Those suffering from right sided foci epilepsy but not left-sided foci, have been found to exhibit decreased performance on an odour-matching task (Abraham and Mathai, 1983), an odour memory test for nameable odours (Carroll, Richardson and Thompson, 1993) and Olfactory Identification (Kohler, Moberg, Gur, O'Connor, Sperling and Doty, 2001). Bilateral deficits have been reported for smell discrimination, short and long-term odour memory, and odour naming (Martinez, Cain, de Wijk, Spencer, Novelly and Sass, 1993).

HIV.

Olfactory dysfunction in those with HIV has been observed by several investigators (Westervelt, McCaffrey, Cousins, Wagle and Haase, 1997; Hornung, Kurtz, Bradshaw, Seipel, Kent, Blair and Emko, 1998). Given that HIV is a progressive disease and often ends in dementia (which itself causes olfactory impairment) and a host of other concomitant malignancies it is not surprising that results are mixed. A few studies have found no olfactory dysfunction (Mueller, Temmel, Quint, Rieger and Hummel, 2002) while others have found differences in tasks such as Identification, detection and recognition.

An excellent study by Zucco and Ingegneri (2004) examined a large spectrum of HIV+ patients at various stages of severity (from asymptomatic HIV+, to HIV+ and AIDS with a severe degree of dementia) by olfaction. Their results, as hypothesized, demonstrated that those with HIV do have decreased olfactory ability, which was concomitantly related to HIV severity. Concerning tasks, most patients did well on the olfactory recognition task, however those patients at a more serious stage in the two groups experiencing dementia did poorly. It is suggested that their cognitive deficits are not only central but also global peripheral.

As the Olfactory Identification task requires a very high level of cognitive processing it was anticipated that deficits would manifest much earlier in the disease process. This in fact is what the research demonstrated, with Olfactory Identification presenting early in the disease process and deficits being proportional to severity.

Huntington's disease.

Huntington's disease is a rare abnormal neurodegenerative disorder in which the afflicted individual exhibits involuntary muscle movements (chorea) and mental deterioration resulting in dementia (Mitchell, Heims, Neville and Rickards, 2005). It is considered that Huntington's is a frontostriatal dementia with the disease initially affecting the basal ganglia and the head of the caudate nucleus (Hawkes, 2003). This deterioration begins early in life and is known to extend to the olfactory processing areas (Nordin, Paulsen and Murphy, 1995) early in the disease process. The olfactory structures most affected are the entorhinal cortex, thalamus, parahippocampal gyrus and caudate nucleus (Barrios, Gonzalez, Favila, Alonso, Salgado, Diaz and Fernandez-Ruiz, 2007).

Those with Huntington's disease exhibit olfactory dysfunction namely Olfactory Threshold (Moberg and Doty, 1997); Discrimination (Nordin, Paulsen and Murphy, 1995); recognition (Moberg, Pearlson, Speedie, Lipsey, Strauss and Folstein, 1987); and Identification (Moberg and Doty, 1997). Interestingly Olfactory Discrimination occurs

significantly prior to the onset of motor or cognitive deficits (Hamilton, Murphy, and Paulsen, 1999).

A study by Larsson, Lundin and Robins-Wahlin (2006) who examined asymptomatic carriers of the Huntington disease mutation found that these gene carriers were impaired in accurately discriminating odour quality and that their impairment was directly proportional to degree of mutation. As Odour Discrimination is an olfactory working memory task and requires a considerable cognitive load, other cortical areas are recruited such as the hippocampus and caudate regions (Savic, Gulyas, Larsson, and Roland, 2000).

Another interesting finding is that those with Huntington's disease do not recognise disgust in the facial and vocal expressions of others and they do not respond in disgust to foul smelling odours (Mitchell, Heims, Neville, and Rickards, 2005).

Korsakoff's syndrome.

For some decades, it has been known that those with Korsakoff's syndrome have profound olfactory perceptual deficits. This includes odour quality discrimination, (Potter and Butters, 1979); Odour Discrimination (Mair, Capra, McEntee and Engen, 1980); sensitivity (Threshold) (Doty, Shaman and Dann, 1984); and Odour Identification (Mair, Doty, Kelly, Wilson, Langlais, McEntee and Vollmecke, 1986).

Another study by Rupp, Kurz, Kemmler, Mair, Hausmann, Hinterhuber and Fleischhacker (2003) examined olfactory functioning in nonamnestic and nondemented alcohol dependent patients. Their results indicated that alcohol dependent patients had impaired olfactory functioning in comparison to controls on Threshold, Discrimination and Identification tests. Lower olfactory scores were associated with length of dependency (patients and controls premorbid IQ scores were comparable). Other research by Rupp, Fleischhacker, Drexler, Hausmann, Hinterhuber and Kurz (2006) concluded that olfactory deficits amongst the alcohol dependent are likely due to prefrontal cognitive dysfunction

and in particular, Olfactory Discrimination deficits are associated with executive functional impairment.

Dementia with Lewy bodies (DLB).

Dementia with Lewy bodies (DLB) is the most common neurodegenerative disorder following multi-infarct dementia and Alzheimer's. Its symptoms include hallucinations, tremor, muscle rigidity, hypokinesia, involuntary movement and abnormal posture. Lewy bodies are neuronal inclusion bodies, which appear to be markers for neuronal loss and are situated in the cerebral cortex (Sadock and Sadock, 2003). The disease is typically rapid in its course with early onset of confusion, drug sensitivity, visual hallucinations and subsequent dementia.

Olfactory dysfunction is a feature of DLB with many authors demonstrating various losses. For instance, Liberini, Parola, Spano and Antonini (1999) observed severe impairment in Olfactory Identification and Threshold detection in those with DLB which occurred independently of the stage of the disease. Other authors such as Gilbert, Barr and Murphy (2004) have also noted poor Odour Discrimination in comparison to elderly controls. They also found that those with DLB when compared to those with Alzheimer's had significantly lower Olfactory Threshold and familiarity scores, thus this difference may assist in determining variants of dementia.

Westervelt, Stern and Tremont (2003) also noted significant Olfactory Identification deficits in those with DLB and found that these deficits are significantly more prevalent and severe than those with Alzheimer's.

Multiple sclerosis.

Multiple sclerosis (MS) is a progressive disorder and is categorised as a major demyelination disorder due to the disseminated demyelination of nerve fibres in the brain and spinal cord. Typically a patient will have multiple episodes of symptoms. Initially the presentation of symptoms may include abnormal sensations in the extremities or on one

side of the face, muscle weakness, vertigo and visual disturbances before progression to the more insidious cognitive and behaviour changes. These symptoms are pathophysiologically related to multifocal lesions in the white matter of the brain. The aetiology of this disorder is unknown however, it is considered that a slow viral infection and disruption of the immune system are factors (Sadock and Sadock, 2003).

Hawkes, Shephard and Kobal (1997) conducted a study to determine whether olfaction would be affected by MS. Their results indicated that all patients exhibited lower scores on an Olfactory Identification test than matched controls and they concluded that there is olfactory dysfunction in those with MS. A study by Doty, Li, Mannon and Yousem (1998) found that approximately 40% of those with MS had Olfactory Identification deficits and by using MRI screening noted that this loss was commensurate with plaque load within olfactory related central brain regions such as the inferior frontal and temporal lobes. A similar MRI and olfaction study found a significant relationship between lesion loads in the white matter of the olfactory brain region and smell loss (Zorzon, Ukmar, Bragadin, Zanier, Antonello, Cazzato and Zivadinov, 2000).

Another study examining the relationship between MS and olfaction found a correlation between severity of neurological impairment and Olfactory Identification score. However, very few reported olfactory dysfunction, indicating that most were unaware of the diminution in their sense of smell (Zivadinov, Zorzon, Monti Bragadin, Pagliaro and Cazzato, 1999).

Parkinson's disease.

Parkinson's disease is a slow progressive multisystem degenerative neurological disorder of unknown etiology. Typically, it presents in those aged over 60 and is characterized by resting tremor, muscle rigidity and weakness, mask like face, shuffling gait, forward flexion of the trunk and loss of postural reflexes. The disease initially begins in a few predisposed nerve cells with the formation of Lewy bodies and proliferates in a

topographically predictable manner with the autonomic, limbic, and somatomotor systems becoming the most impaired (Braak, Ghebremedhin, Rub, Bratzke and Del Tredici, 2004).

Braak, Ghebremedhin, Rub, Bratzke and Del Tredici (2004) have developed an excellent six histopathological stage system of Parkinson's disease. In the first presymptomatic stage (1 and 2) Lewy Body pathology is restricted to the medulla oblongata / pontine tegmentum and olfactory bulb / anterior olfactory nucleus. Stage 3 and 4 is when patients first notice symptoms which increasingly progress. This is the stage when Lewy bodies become evident in the substantia nigra and other nuclear grays of the midbrain and forebrain. Stage 5 and 6 is the end stages where the Lewy Bodies affect the neocortex and the disease is most pronounced.

As the olfactory bulb and anterior olfactory system is one of the first casualty sites of neuropathological abnormality, it is not surprising that olfactory dysfunction is an early and frequent symptom noted in Parkinson's disease. Over thirty years ago Ward, Hess and Calne (1983) documented abnormalities of odour detection, differentiation and Identification deficits in those with Parkinson's disease and since then it has become an established medical idiom that olfactory dysfunction is one of the primary and most prevalent clinical manifestations of this disorder (Berendse and Ponsen, 2006). For instance a 1998 meta-analysis of olfactory functioning in Alzheimer's and Parkinson's Diseases concluded that there are severe olfactory deficits in each of the olfactory domains namely, Threshold, Discrimination, and Identification (Mesholam, Moberg, Mahr and Doty, 1998).

Although Olfactory Identification is significantly impaired in those with Parkinson's compared to controls, the ability to identify some odours such as orange and clove remains intact, where-as the odours of pineapple, aniseed, liquorice (Daum, Sekinger, Kobal and Lang, 2000), pizza, wintergreen (Gelb, Oliver and Gilman, 1999) gasoline, banana, smoke and cinnamon (Double, Rowe, Hayes, Chan, Blackie, Corbett,

Joffe, Fung, Morris and Halliday, 2003) are regularly misidentified. Doty, Deems and Stellar (1988) have noted that olfactory dysfunction is independent of either disease duration or severity.

Interestingly there is a doubling of dopaminergic neurons in the olfactory bulb of those with Parkinson's disease (Huisman, Uylings and Hoogland, 2004), where-as there is a distinct lack of dopamine in the nigrostriatal projection and this is the reason for the motor deficits (Ehringer and Hornykiewicz, 1960). It has been postulated that because dopamine inhibits olfactory transmission in the olfactory glomeruli this excess of dopamine may be the cause of olfactory dysfunction in those living with Parkinson's disease (Huisman, Uylings and Hoogland, 2004).

Although impairment of olfactory function contributes to a diagnosis of Parkinson's disease in the initial symptomatic stages (stages 3 and 4) other studies are assessing its prognostic value in the preclinical stage.

Results from a prospective study of first degree relatives of those with Parkinson's indicate that of those with idiopathic hyposmia, 13% have now developed clinical Parkinson's. Conversely, none of the normosmic relatives in the cohort have developed Parkinson's (Berendse and Ponsen, 2006). Similar results have been found in other studies examining first degree relatives (Ponsen, Stoffers, Booij, van Eck-Smit, Wolters and Berendse, 2004). These results suggest that those suffering idiopathic olfactory dysfunction are at greater risk of developing Parkinson's disease.

It is now considered that the presence of Lewy bodies in the brain of those without Parkinson's or dementia is a presymptomatic stage of Parkinson's disease. A study by Ross, Abbott, Petrovitch, Tanner, Davis, Nelson, Markesbery, Hardman, Masaki, Launer and White (2006) examined the brains of 164 males at autopsy for Incidental Lewy Bodies (asymptomatic of Parkinson's or Dementia) who had also previously undertaken a test of olfaction. They found that those who did very poorly on the Olfactory Identification test

were 11 times more likely to have incidental Lewy bodies than those who did very well. They concluded that olfactory dysfunction is associated with Incidental Lewy Body disease.

A study of an aged community based population who were free of clinical Parkinson's disease were followed for up to 8 years. This study found that impaired Olfactory Identification often predated clinical Parkinson's disease in males by at least 4 years. The researchers concluded that olfactory testing may be a useful screening tool for identifying those at high risk for development of Parkinson's (Ross, Petrovitch, Abbott, Tanner, Popper, Masaki, Launer and White, 2008).

Schizophrenia.

According to the *DSM-IV-TR* schizophrenia is a disorder characterised by a deteriorating ability to function adequately socially, occupationally and / or in everyday life due to the presence of two or more of the following symptoms which have been present for at least a period of one month.

- Gross distortions of reality via prominent delusions or hallucinations
- Disturbance of language and communication
- Grossly disorganised movement
- Inappropriate emotional expression (American Psychiatric Association, 2000).

Symptoms vary greatly between individuals and differ in intensity. For instance, some individuals with schizophrenia have deteriorating cognitive capacities and others do not, thus presentations can differ significantly. However, despite more than 100 years of research, the aetiology of schizophrenia still remains unknown.

At present, the prevailing hypothesis is that schizophrenia is a neurodevelopmental disorder, which is due to small, but subtle abnormalities of the nervous system which occur during prenatal or neonatal development and later affect brain functioning. This view has been supported by the following findings:

- Much of the brain abnormality is already present at the time of the first episode,
- Impairment remains stable over time
- Some prenatal and neonatal abnormalities which impair brain development are correlated with schizophrenia (Premkumar and Sharma, 2005).

To date many structural MRI studies of those with schizophrenia have demonstrated the following:

Decrements in the volume of the olfactory bulb in both those with schizophrenia and first degree family members (Turetsky, Moberg, Arnold, Doty and Gur, 2003). A meta-analysis by Shenton, Dickey, Frumin and McCarley (2001) in which they examined 193 peer reviewed articles, noted that there were reported in the majority of articles, abnormalities in the grey matter in the prefrontal, orbitofrontal, medial temporal lobe, amygdala, parietal lobe and hippocampal areas of the brain.

Another meta-analysis of those with first episode schizophrenia noted increased ventricular volumes and whole brain and hippocampal volume reduction relative to healthy controls (Steen, Mull, McClure, Hamer and Lieberman, 2006).

Also cortical atrophy, disruption in the integrity of the cortical white matter and abnormally pronounced aging effects on brain anatomy have been noted (Andreone, Tansella, Cerini, Rambaldelli, Versace, Marrella, Perlini, Dusi, Pelizza, Balestrieri, Barbui, Nose, Gasparini and Brambilla, 2006).

Additionally, there is strong to moderate evidence for subcortical abnormalities (Bersani, Paolemili, Quartini, Clemente, Gherardelli, Iannitelli, Di Biasi, Gualdi and Pancheri, 2007).

Furthermore a meta-analysis of studies conducted on the brain volumes of relatives of patients with schizophrenia found that first degree relatives of those with schizophrenia had smaller hippocampal volume, less grey matter and larger third ventricle volume than healthy matched controls (Boos, Aleman, Cahn, Pol and Kahn, 2007).

Given the degree of abnormality in various brain regions affected by schizophrenia especially the frontal lobe, temporal lobe and limbic system, regions that are secondary olfactory processing sites, one would envisage olfactory dysfunction in those with schizophrenia. In fact, there is a considerable amount of evidence that those with schizophrenia do have global olfactory deficits. Moberg, Agrin, Gur, Gur, Turetsky and Doty (1999) conducted a meta-analytic review of the literature concerning olfaction and schizophrenia. Their results indicated that there are substantial olfactory deficits across all aspects of olfaction, including Threshold sensitivity, Discrimination, memory and Identification. This result was despite factors of gender, medication status, and smoking. Similar results were obtained in the review conducted by Rupp (2003). Another study by Rupp, Fleischhacker, Kemmler, Kremser, Bilder, Mechtcheriakov, Szeszko, Walch, Scholtz, Klimbacher, Maier, Albrecht, Lechner-Schoner, Felber and Hinterhuber (2005) noted that those with schizophrenia in comparison to controls had reduced bilateral hippocampal and amygdala volumes and that smaller hippocampal volume was associated with poorer Olfactory Discrimination. Global olfactory deficits typically increase progressively over the course of the disorder (Moberg, Doty, Turetsky, Arnold, Mahr, Gur, Bilker and Gur, 1997).

Other features of schizophrenia have been associated with inferior Odour Identification scores such as: Social deficits and poor hygiene (Brewer, Edwards, Anderson, Robinson and Pantelis, 1996); Deficit Syndrome (meta-analysis) (Cohen, Saperstein, Gold, Kirkpatrick, Carpenter and Buchanan, 2007); and clinical ratings of negative symptoms (Malaspina and Coleman, 2003). Other studies have found impaired familiarity and edibility judgments of everyday odours (Rupp, Fleischhacker, Kemmler, Oberbauer, Scholtz, Wanko and Hinterhuber, 2005) as well as higher ratings of pleasantness in those with schizophrenia (Rupp, Fleischhacker, Kemmler, Oberbauer, Scholtz, Wanko and Hinterhuber, 2005; Doop and Park, 2006).

As in adults with schizophrenia, Olfactory Identification deficits also exist in early onset psychotic disorders in children and adolescents in comparison to matched control groups (Corcoran, Whitaker, Coleman, Fried, Feldman, Goudsmit and Malaspina, 2005). Other authors have observed deficient olfaction in unaffected relatives of those with schizophrenia. An olfaction study examining monozygotic twins with and without schizophrenia noted that the twin with schizophrenia was globally impaired for olfaction whilst the non affected twin was partially impaired, thus indicating that olfactory dysfunction may be a marker of a genetic vulnerability to schizophrenia (Ugur, Weisbrod, Franzek, Pfuller and Sauer, 2005).

Compton, McKenzie-Mack, Esterberg, Bercu, Kryda, Quintero, Weiss and Walker (2006) note that there are two correlated risk markers for schizophrenia, impairment in both Olfactory Identification and verbal memory and that this is likely due to frontal temporal deficits.

Thus, these findings imply that olfactory regions are affected by schizophrenia; initially as a genetically mediated neurodevelopmental process and also later as part of the sequelae of the progressive pathological neurodegenerative processes involved in schizophrenia. In order to further validate such a hypothesis longitudinal research needs to be performed to investigate olfaction and schizophrenia. A landmark longitudinal study by Brewer, Wood, McGorry, Francey, Phillips, Yung, Anderson, Copolov, Singh, Velakoulis and Pantelis (2003) was conducted where they performed Olfactory Identification tests on 81 participants at high risk of developing psychosis and 31 comparison subjects. Of the 81 high risk subjects, 22 later became psychotic and of these 22, 12 were diagnosed with schizophrenia. Their results demonstrated that there was a significant Olfactory Identification deficit in the 12 ultra high risk subjects prior to the onset of their schizophrenia in comparison to the other groups. They concluded that Olfactory Identification deficits act as a premorbid identifier or trait marker of transition to

schizophrenia but not of psychosis in general. It is hypothesised by this group that Identification deficits are due to a neurodevelopmental delay of portions of the limbic-prefrontal pathways.

Traumatic Brain Injury.

Olfactory disorder following head injury was first described in the medical literature in 1864 by Hughlings Jackson (Swann, Bauza-Rodriguez, Currans, Riley and Shukla, 2006). Although olfactory disorder is more likely to occur after a serious head injury, it can also occur in those with a mild head injury (Mann, 2003). Figures vary but between 5% - 65% of those with a brain injury will be suffering olfactory dysfunction, but this is dependent on the type of injury and severity (Doty, Yousem, Pham, Kreshak, Geckle and Lee, 1997).

An excellent 18 year longitudinal study conducted by Swann, Bauza-Rodriguez, Currans, Riley and Shukla (2006) found that only those with a head injury which caused concussion and at least 5 minutes of post traumatic amnesia or a skull fracture were at risk of subsequent olfactory dysfunction. Callahan and Hinkebein (2002) noted that those with Olfactory Identification deficits are often unaware of their dysfunction and this dysfunction is related to injury severity. In addition, many who have total loss of olfactory ability (anosmia) demonstrate significant impairment in a variety of frontal-lobe mediated executive functions, as well as greater functional disability (Callahan and Hinkebein, 1999).

There are numerous head and face traumas which can cause anosmia or partial loss of olfactory ability and these are typically caused by motor vehicle accidents and falls. This may involve a direct insult to the olfactory epithelium or even the inhalation of toxic fumes. Due to the epithelium's regenerative capacity, the insult may be temporary or in severe cases permanent. Other causes include damage to the nasal cavity, but the most common mechanism is due to the tearing of olfactory fila, which pass through the ethmoid

bone at the cribriform plate (Collet, Grulois, Bertrand and Rombaux, 2009). Any sudden coup or contre coup forces which move the brain within the cranium can easily tear fragile olfactory fibres. In addition, the cribriform plate is very delicate and easily fractured by a sharp upward blow similar to that which a person receives when striking their nose on the dashboard of a car during an accident. Such fractures commonly shear olfactory fila.

Injury to the frontal lobes especially of the olfactory bulb, intra – parenchymal haemorrhage (Reiter, DiNardo and Costanzo, 2004) and damage to central olfactory brain processing regions (Costanzo and Zasler, 1992) due to closed head injury will also cause olfactory disorder. Typically anterior temporal lobes and the orbital frontal regions are damaged in closed head injury; areas associated with olfactory processing (Costanzo and Zasler, 1992).

Olfactory Identification scores have been shown to be related to the severity of closed head injury with olfactory scores relating to Glasgow Coma Scale Scores, posttraumatic amnesia and radiological abnormalities (Green, Rohling, Iverson and Gervais, 2003). Another study by Rombaux, Mouraux, Bertrand, Nicolas, Duprez and Hummel (2006) found a correlation between olfactory function and olfactory bulb volume in those with traumatic head injuries.

An important study conducted by Savage, Combs, Pinkston, Advokat and Gouvier (2002) compared olfactory functioning amongst those with left and right CVA (lesion to the temporal lobe cortex), Traumatic Brain Injury (more orbitofrontal lesion than temporal lobe) and controls. Their results demonstrated that those most impaired were those with CVA's as they had deficits in both odour Identification and odour recognition, where-as those with Traumatic Brain Injury demonstrated impairment on odour Identification tasks but performed much better on the delayed recognition task. These results indicate that the temporal olfactory cortical areas are involved in the initial processing of odours and for recognizing an odour as novel or familiar, but that odour information is then relayed to the

OFC, which is critical to the process of identifying specific odours. Thus if damage to primary olfactory areas, e.g., temporal lobe, occurs there is a restricted amount of information being conducted to the orbitofrontal region. Thus, injuries to the temporal lobes result in both recognition and Identification deficits. When recovery occurs, it is usually within a year of the injury. Rates of recovery or partial recovery of olfaction one year post traumatic brain injury vary from 10% (Jimenez, Sundrani, Barone, 1997; Reden, Mueller, Mueller, Konstantinidis, Frasnelli, Landis and Hummel, 2006) to 25% to 35% (Mori, Aiba, Sugiura, Matsumoto, Tomiyama, Okuda, Okigaki and Nakai, 1998; Duncan and Seiden, 1995; Doty, Yousem, Pham, Kreshak, Geckle and Lee, 1997).

The proposal that neuronal olfactory tracts are capable of regeneration is based on morphological and electrophysiological examination of animals. Kern, Quinn, Rosseau and Farbman (2000) in a histopathological analysis of the olfactory bulbs and tracts of humans noted that there was some degree of neuronal regeneration in the cribriform region, however this was limited by fibrosis and scarring, thus preventing the reconnection of sprouting axons and the olfactory bulb.

Psychiatric

Depression.

There have been several studies conducted to determine whether there are Olfactory Identification deficits associated with depression. But unlike neurological disorders the majority of these studies have found no significant differences between depression and control groups (Amsterdam, Settle, Doty, Abelman and Winokur, 1987; Warner, Peabody and Csernansky, 1990; Solomon, Petrie, Hart and Brackin, 1998; Lombion - Pouthier, Vandel, Nezelof, Haffen and Millot, 2006) though a few studies such as that by Serby, Larson and Kalstein (1990) have done so. A definitive study by Pause, Raack, Sojka, Goder, Aldenhoff and Ferstl (2003) using a highly calibrated olfactometer and EEG data demonstrated unequivocally that in their sample there were no differences

between controls and depressed. However, they did find significant strongly reduced deficits in Odour Threshold in the acute phase of those with major depression in comparison to the control groups. This confirms much other research, which has found similar results (Pause, Miranda, Goder, Aldenhoff and Ferstl, 2001; Lombion-Pouthier, Vandiel, Nezelof, Haffen and Millot, 2006). In addition, the study by Pause, Miranda, Goder, Aldenhoff and Ferstl (2001) noted a predictive relationship between lowered Threshold and increased depression scores. After treatment Olfactory Threshold scores improved but not significantly, which shows that odour processing is still impaired and that it is likely a trait marker in those who suffer from major depression.

It has been postulated by Martzke, Kopala, and Good (1997) that the Olfactory Threshold test provides reliable information about the functionality of the primary sensory level of stimulus processing. This involves cortical areas such as the piriform cortex and amygdala (Gottfried, Deichmann, Winston, and Dolan, 2002). In the case of those with major depression it indicates that there is likely an inability to encode olfactory input. In contrast the Identification and Discrimination olfactory tests are indicative of secondary or higher order stimulus processing i.e., insula and the orbital frontal cortex (Gottfried, Deichmann, Winston, and Dolan, 2002) and in those with depression it appears that the cognitive evaluative processing factor remains intact. Pause, Miranda, Goder, Aldenhoff and Ferstl (2001) have hypothesised that the olfactory bulb in those with major depression is dysfunctional and could be the reason for lowered olfactory sensitivity and for an amplified sense of fear and sadness due to a disinhibition of the amygdala.

Finally, a study by Lombion-Pouthier, Vandiel, Nezelof, Haffen and Millot (2006) noted a counter intuitive result. They found that those who suffered from depression consistently and significantly over-evaluated the pleasantness of odours.

Intermittent Explosive Disorder.

A search of Pub Med, Google Scholar and PsycINFO indicated that there was only the one article on the subject of olfaction and Intermittent Explosive Disorder (IED). The authors of the article Best, Williams and Coccaro (2002) hypothesized that subjects with IED would exhibit on a battery of tests, performances similar to those people with lesions to the orbital/medial prefrontal cortex. The hypothesis was confirmed with results indicating that those with IED did indeed exhibit significantly impaired performance. Tests included the University of Pennsylvania Smell Identification Test and the results demonstrated that those with IED were significantly impaired relative to controls. An interesting finding was that performance on the facial recognition test was impaired with emotions such as "anger" "disgust" and "surprise" not being recognized, and neutral faces being more likely to be identified as "disgust" or "fear."

Obsessive-compulsive disorder.

There have been several studies where olfaction and obsessive compulsive behavior have been examined. One investigation conducted by Barnett, Maruff, Purcell, Wainwright, Kyrios, Brewer and Pantelis (1999) concluded that although those with obsessive-compulsive disorder (OCD) did not suffer from anosmia (reduced threshold or sensitivity) but they did have as hypothesised impaired spatial cognition and Olfactory Identification. This is deemed to be due to a disruption of processing in the OFC, which is an area of the brain implicated in the pathology of OCD.

Other investigators Hermesh, Zohar, Weizman, Voet and Gross-Isseroff (1999) who examined Olfactory Discrimination and Threshold did not find any significant differences between those with OCD and controls. The non-significant result in the difference between Threshold levels in the two groups is consistent with the results from other studies. However although the hypothesised result of a difference between the two groups in Olfactory Discrimination did not eventuate there was an unexpected significant

within group difference. In the OCD group those most severely affected were most likely to accurately discriminate the more difficult part of the quality discrimination task. This finding needs to be repeated before any conclusions can be drawn.

Seasonal Affective Disorder.

Seasonal Affective Disorder (SAD) is characterised by depression, which occurs at the same time each year with winter being the predominant period (Bauer and Dunner, 1993). The *DSM- IV-TR* categorizes SAD not as a distinct and separate mood disorder, but as a specifier of major depression (American Psychiatric Association, 2000). This seasonal pattern specifier may be applied to the pattern of depression in bipolar disorder or major depression. SAD can be safely treated with light therapy, which is more efficacious if administered in the morning (Lurie, Gawinski, Pierce and Rousseau, 2006).

To date there is no evidence for Olfactory Identification or Discrimination deficits in those with SAD. This is congruent with the findings of other olfaction studies amongst those suffering from depression. However, there are some findings suggestive of increased Olfactory Threshold sensitivity amongst those with SAD in remission. For instance, a study by Nawab, Miller, Dale, Greenberg, Friedman, Chrousos, Straus and Rosenthal (2000) indicated that patients with SAD self-reported a greater sensitivity to chemicals than controls. Another study by Postolache, Wehr, Doty, Sher, Turner, Bartko and Rosenthal (2002) noted that those with SAD in comparison to controls had significantly higher Olfactory Thresholds when in remission.

PTSD.

Prior to the current investigation three studies had been reported examining PTSD and olfactory function. The first study, by Vasterling, Brailey and Sutker (2000), tested Vietnam veterans and found Olfactory Identification deficits in veterans with PTSD in contrast to veterans without PTSD.

Specifically the study by Vasterling, Brailey and Sutker (2000) examined Olfactory Identification and cognitive functioning in three groups of Vietnam veterans. These groups were comprised of those who:

- Served in the war zone and were diagnosed with PTSD;
- Served in the war zone but were without PTSD and other Axis I mental disorders;
- Did not serve in the war zone and did not suffer PTSD or other Axis I mental disorders.

Their results demonstrated that those who were diagnosed with PTSD were significantly less proficient in the odour Identification and verbal learning task than either of the other groups. The other cognitive tests, which were sensitive to dorsolateral prefrontal and mesial temporal functioning, were not significantly different. The authors concluded that these results further support the accumulating evidence of OFC dysfunction in those with PTSD as Olfactory Identification is constitutively processed by the OFC. Thus given that Vietnam veterans who served in the war zone but without PTSD did not have Olfactory Identification deficits, suggests that it is the effect of the PTSD response to trauma which precipitates the olfactory deficits. However, this proposition remains to be tested.

The second similar study by Dileo, Brewer, Hopwood, Anderson and Creamer (2008) also examined Vietnam veterans. However, the authors added a self-reported measure of impulsivity and aggression. Their results confirmed the findings of Vasterling, Brailey and Sutker (2000) except that they also found that low Olfactory Identification correlated with impulsivity and aggression. The authors in both studies have concluded that the Olfactory Identification deficits in those with PTSD are likely due to an element of the underlying pathophysiology of PTSD, possibly OFC dysfunction (Vasterling, Brailey and Sutker, 2000; Dileo, Brewer, Hopwood, Anderson and Creamer, 2008).

The third study, deemed an exploratory study by the authors Croy, Schellong, Joraschky and Hummel (2010), examined adults with a history of child maltreatment. They found that those with childhood maltreatment and a current diagnosis of PTSD in comparison to those with maltreatment and no PTSD exhibited enhanced odour Identification. Other findings also included a faster response time to unpleasant olfactory stimuli in those with PTSD but no difference between the groups in Olfactory Threshold levels.

The findings of the study by Croy, Schellong, Joraschky and Hummel (2010) in which those with PTSD had increased Olfactory Identification are in complete contrast to the findings by the previous authors. Croy, Schellong, Joraschky and Hummel (2010) postulate that as Odour Identification reflects central processing then enhanced orbitofrontal functioning may-be the reason for this result. Attempting to reconcile the disparate findings of these studies is difficult and demonstrates that further research is required to clarify the relationship between PTSD and olfaction.

To date there has been no research to clarify the status of olfactory functioning before the onset of PTSD. However based on the outcome of other longitudinal studies which have examined olfactory precursors to neurological disorders, and the results of (Dileo, Brewer, Hopwood, Anderson and Creamer, 2008; Vasterling, Brailey and Sutker, 2000), it was hypothesised that olfactory deficits would predict the onset of PTSD. As there is a considerable overlap of the olfactory and limbic systems, one may hypothesise that dysfunction in one system would be manifest in the other. Thus, an individual with a compromised or vulnerable limbic system may present with concomitant olfactory deficits.

Thus, the above studies raise some very profound questions, which the present study will attempt to answer. For instance:

- Firstly, is it the effect of the PTSD response, which causes OFC dysfunction?

- Alternatively, do those who develop PTSD already have a pre-existing compromised OFC with the result that they are predisposed or vulnerable to trauma and its aftermath?
- Or possibly is it a combination of both factors? For instance are those who have diminished or borderline OFC functioning predisposed and vulnerable to PTSD (with concomitant low Olfactory Identification scores); and upon being traumatised the OFC becomes increasingly sensitised and further compromised (with concomitant significantly lower Olfactory Identification scores)?
- How soon after the traumatic event do OFC compromise and concomitant low Olfactory Identification scores begin to occur?

Therefore, this study offers a valuable contribution to the literature determining whether olfactory dysfunction is a predictive vulnerability marker of PTSD or a feature of PTSD. If it is the former, it has the potential to inform PTSD prevention and treatment.

CHAPTER 3: METHODS

In this study a between subjects and within subjects design was used to compare the psychological and psychophysiological functioning of trauma victims with PTSD and trauma victims without PTSD over a 12 month period. The aspects of psychological and psychophysiological consideration include ASD, PTSD and Olfactory functioning as well as demographic information. These aspects of functioning were assessed via a number of standardised instruments listed and described below. These measures were obtained initially prior to discharge from the Royal Adelaide Hospital, at 3 months, and again at 12 months.

Participants in this study were part of a multi-centre study described in O'Donnell, Varker, Creamer, Fletcher, McFarlane, Silove, Bryant and Forbes (2013).

Participants

Inclusion Criteria

Patients who were admitted to the Trauma Department of the Royal Adelaide Hospital having sustained a physical injury and who met inclusion criteria were recruited into the study over a 24-month period. The following criteria determined inclusion:

- An admission to the Trauma department of the hospital for 24 hours or greater.
- Aged between 16 and 70 years.
- Having a reasonable understanding of the English language (determined by the ability to read and comprehend the participant information sheet and consent form).
- Resident of Australia.

The reasons for the above inclusion criteria were as follows. The first priority was for patients to be medically assessed and treated by the Trauma service. After treatment patients could be recruited into the study, however admissions of less than 24 hours meant that it was highly probable that the majority of these patients would be discharged before

being recruited despite the admission list being reviewed every 24 hours. Patients who were 16 years of age or younger were sent directly to the Women's and Children's Hospital and not assessed at the Royal Adelaide Hospital Trauma service. Those over 70 were considered more marginal candidates for a longitudinal study due to possible increased ill health and memory issues. An understanding of both written and spoken English was an essential requirement as there were three self-report booklets to be completed at the initial, 3 month and 12 month stage; clinical and telephone interviews to be comprehended and informed consent to be established in order to be a participant in the study. Finally, patients without residential status were considered problematic for follow up due to their itinerant circumstances.

Exclusion Criteria

Patients were excluded from the study if any of the following criteria applied:

- Non traumatic injury (Appendix A for definitions)
- Death
- Moderate or severe brain injury (Appendix B for definitions)
- Non direct emergency admission - admissions whereby the individuals have not come directly to the trauma service. (This included admissions via GP or home and usually occurs with minor injuries. It did not include patients with severe injuries admitted via a stabilising hospital such as a rural hospital)
- Satellite admission. (A particularly small number of patients were admitted for very short periods because they had minor injuries but predominantly where adverse social circumstances preceded the hospital admission)
- Admission was due to a deliberate act of self-poisoning
- Cognitive impairment
- Under Police guard

- Current psychotic disorder
- Discharged from the Trauma Department whilst actively suicidal.

The above list was also the order of exclusion. These exclusion criteria were applied as these factors could affect the outcome of the study. For instance, patients who died, incurred moderate or severe brain injury or were significantly cognitively impaired were not in a position to understand the study and give informed consent. Patients having performed a nonviolent act of self-harm such as poisoning were excluded as the premeditated nature precluded the possibility of a diagnosis of PTSD. Patient who were psychotic or actively suicidal were detained under the mental health act and not able to provide informed consent.

Once participants were recruited, demographic information was obtained from a self-report questionnaire. Questions pertaining to marital status, income, employment, hours of work, and days out of role were asked. The questions were replicated from The National Survey of Mental Health and Wellbeing (NSMHW) conducted by the Australian Bureau of Statistics (1998) in 1997 and the Australian Census (Australian Bureau of Statistics, 2001) which have normative data.

Variables and Measures

Independent and Dependent Measures

The independent variable in this study was clinical diagnosis: PTSD or no clinical diagnosis of PTSD. The dependent variables (DV's) in this study were:

1) Olfactory Identification, 2) Olfactory Discrimination and 3) Olfactory Threshold.

Independent Variable

PTSD.

PTSD diagnosis was obtained from a clinical interview using Clinician Administered PTSD Scale (CAPS). The Clinician Administered PTSD Scale (Blake, Weathers, Nagy, Kaloupek, Charney and Keane, 1998) was administered to participants to assess Posttraumatic Stress Disorder relative to the injury producing event. This structured clinical interview is one of the most extensively used tools for diagnosing PTSD and measuring PTSD severity. It also has demonstrated excellent reliability and validity (Weathers, Keane and Davidson, 2001). It consists of 17 questions, each relating to specific *DSM-IV-TR* PTSD symptoms and five additional questions assessing guilt (two questions) and dissociation (three questions). Although the CAPS has most frequently been used to assess PTSD with additional dissociative questions, it has also been applied to assess ASD (O'Donnell, Creamer, Pattison and Atkin, 2004). In the current study, PTSD was scored using the "1 - 2 rule" (i.e., diagnostic criteria were met for each symptom if frequency ≥ 1 and intensity ≥ 2) (Weathers, Keane and Davidson, 2001). Frequency and intensity scores were summed to obtain an overall PTSD severity score. It was administered on three occasions during the study: In the acute setting, at 3 and 12 months, and on each occasion it was only relevant to the event that caused the injury. The CAPS has been shown to be equally as valid conducted by telephone as face-to-face interview (Aziz and Kenford, 2004).

Dependent Variables

Olfactory Functioning was assessed via the "Sniffin' Sticks" method. "Sniffin' Sticks" is an olfactory test battery commercially available and is based on pen-like odour dispensing devices. In order for the odour to be presented, the cap was removed from the pen and the pen's felt tip placed approximately 2 cm directly under and in the middle of both nostrils for approximately 3 seconds. Separate testing of each nostril is possible but

in the current study, the tests were always performed birhinally. “Sniffin’ Sticks” are comprised of three subtests of olfaction: Threshold, Discrimination and Identification (Hummel, Sekinger, Wolf, Pauli and Kobal, 1997); (Kobal, Hummel, Sekinger, Barz, Roscher and Wolf, 1996).

Prior investigators such as Cain, Gent, Goodspeed and Leonard (1988) and Doty, Marcus and Lee (1996) have documented the integrity of “Sniffin’ Sticks” as an olfactory measurement, including its test retest reliability and its validity in comparison to other more established tests such as the Connecticut Chemosensory Clinical Research Centre Test (CCCRC) and the CC-SIT. In addition, the good correlation with another established test such as the University of Pennsylvania Smell Identification Test (UPSIT) confirms its validity (Wolfensberger, Schnieper and Welge-Lussen, 2000). As a result, the “Sniffin’ Sticks” have been used in more than a 100 published studies of olfaction (Hummel, Kobal, Gudziol and Mackay-Sim, 2007). Thus many professional organizations in Europe including the German Society for Otorhinolaryngology, Head and Neck Surgery (Kobal, Klimek, Wolfensberger, Gudziol, Temmel, Owen, Seeber, Pauli and Hummel, 2000) and the German Olfactory and Gustology Association have now recommended its use as a standard for olfactory testing (Huttenbrink, 1997).

Testing of participants was in accord with the methods previously published (Hummel, Sekinger, Wolf, Pauli and Kobal, 1997); (Kobal, Hummel, Sekinger, Barz, Roscher and Wolf, 1996).

An assumption of the study was that olfactory functioning is a relatively stable sense. Unless one has a peripheral condition such as nasal disease or a central condition such as a neurological disorder the sense of smell is relatively stable between the ages of 20 and 60 (Doty and Kamath, 2014). As olfactory functioning is unlikely to change significantly in the space of a week it was assumed that olfactory functioning at hospital admission was likely to approximate olfactory functioning prior to trauma.

Olfactory Identification.

Odour Identification was assessed by the presentation of 16 common odours via pens. Participants were asked to identify each particular odour and could choose the correct answer from a list of four odours. The interval between each odour presentation was approximately 30 seconds and participants were able to sample the odour as often as required. Potential score range was from 0 – 16.

Olfactory Discrimination.

The discrimination task involved the presentation of three odourants via pens, two of which smelt the same and one being an odd one out. The participant's task was to identify which odour was the odd one out. 16 triplets were presented. Odourants were similar in respects of intensity and hedonicity. Participants could only sample the odours once. The presentation of triplets was separated by approximately 30 seconds and the interval between individual sticks about 3 seconds. Potential score range was from 0 – 16.

Olfactory Threshold.

The Threshold test for n – butanol (Cain and Rabin, 1989) was assessed via a triple forced choice procedure. Thus, three pens were presented in random order with two pens containing the solvent and a third pen the identified odourant at a certain dilution. The participant was required to recognise the identified odourant. 16 dilutions were presented in ascending order starting from the 4% n – butanol solution. Three pens were presented at intervals of 20 seconds. When a mistake was made the process was reversed until the odour was correctly identified twice. At that point, the process was again reversed until a mistake was made where upon it would be reversed again. This multiple staircase method has been described by Doty (1991). This process involves seven reversal points however, the geometric mean of the last four staircase reversals became the Threshold estimate. The participants score ranges from 0 – 16.

Procedure

The Trauma Department admission lists were reviewed daily for new admissions. All those patients meeting exclusion criteria were removed from the list. Those meeting inclusion criteria were added to the list. Participants were randomly selected from the list using an automated numerical stratified random assignment procedure (see Appendix C for details of this procedure).

Once a potential participant was identified, they were approached and a lucid explanation and description of the study was provided with a written participant information sheet. Once informed written consent was obtained, the structured clinical interview was administered. The testing time was of 45 – 60 minutes duration. This was followed by the tests of olfaction, which took approximately 40 minutes to complete.

At approximately 3 and 12 months post injury, participants were contacted by telephone to arrange a time, which was convenient for them to be contacted, by telephone to complete the telephone assessments and to have the tests of olfaction administered. Thus, there was the telephone administration of the full CAPS regardless of participant symptom level and testing of olfaction as previously described shortly thereafter. Olfactory testing was conducted at the place most convenient for participants which was mostly in their homes.

Participant Characteristics

There were 202 participants recruited at Time 1 whilst inpatients of the Royal Adelaide Hospital. This was when the initial assessments occurred. Of the participants 157 were male (78 % of the sample) and 45 were female (22 % of the sample). At assessment Time 2, which occurred three months after initial presentation, there were 164 participants engaged with the study. At assessment Time 3, which was twelve months after initial recruitment there were 146 participants. This was a retention rate of 72.27%.

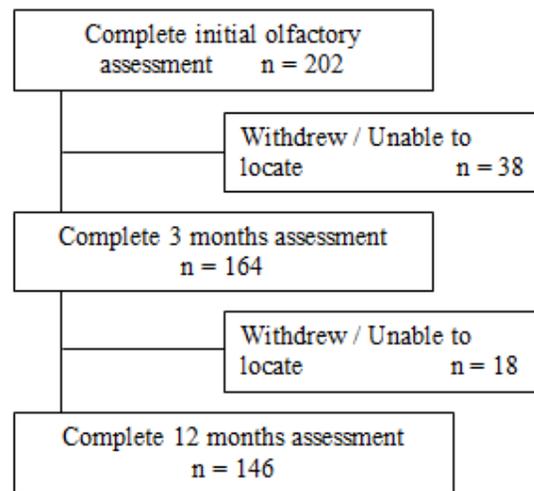


Figure 1. Participant Flow Chart

At assessment Time 1, the mean age of all participants was 38.22 years (SD = 14.33). By gender, the mean age of female participants was 37.83 years (SD = 14.82) and the mean age of male participants was 38.33 years (SD = 14.24). The age range of all participants was from 16 years – 68 years, a span of 52 years. By gender, the age range of female participants was from 17 years – 67 years, an age range of 50 years. The age range for male participants was from 16 years – 68 years, an age range of 52 years.

The prevalence of PTSD amongst participants is described in the results section.

Hypotheses

There were twelve hypotheses investigated in this longitudinal research as set out in Section 1, Part A and Part B; Section 2, Part A and Part B and Section 3, Part A and Part B:

Part A

Firstly previous research (Vasterling, Brailey and Sutker, 2000; Dileo, Brewer, Hopwood, Anderson and Creamer, 2008) has determined that Vietnam veterans with PTSD have Olfactory Identification deficits in comparison to veterans without PTSD.

Based on the above research, the supposition to be determined was whether olfactory functioning deficits predict a diagnosis of PTSD in trauma participants ?

Secondly, as research demonstrates that females are more vulnerable to PTSD than males it was hypothesised that olfactory dysfunction would be greater in females diagnosed with PTSD than the males diagnosed with PTSD.

Thirdly, it was hypothesised that the anticipated deficits of olfactory function in those with PTSD would increase as PTSD progressed over time.

All of the experimental questions were analysed and described by dividing olfactory function into the component parts of:

1. Olfactory Identification (Section 1)
2. Olfactory Discrimination (Section 2)
3. Olfactory Threshold (Section 3).

Part B

Previous research has described how Olfactory Identification deficits are often the first signs of a neurological disorder and may manifest before any of the symptoms of that disorder become evident. For instance in schizophrenia (Brewer, Wood, McGorry, Francey, Phillips, Yung, Anderson, Copolov, Singh, Velakoulis and Pantelis, 2003); Parkinson's (Ross, Petrovitch, Abbott, Tanner, Popper, Masaki, Launer and White, 2008) where deficits often predated clinical Parkinson's disease in males by at least 4 years; and Alzheimer's (Bacon, Bondi, Salmon and Murphy, 1998) where changes in Threshold deficits occurred the year immediately preceding a diagnosis of Alzheimer's disease.

Thus, the central and primary question of this research was whether pre-existing deficits of olfactory functioning would predict a diagnosis of PTSD across time. Specifically do deficits in olfactory function as assessed at time of hospital admission predict the onset of PTSD at Time 2 (3months) or Time 3 (12 months)?

This experimental question was analysed and described by dividing olfactory function into the component parts of:

1. Olfactory Identification (Section 1)
2. Olfactory Discrimination (Section 2)
3. Olfactory Threshold (Section 3)

By clustering the hypotheses into the olfactory functional components namely:

- Section 1 Olfactory Identification score
- Section 2 Olfactory Discrimination score
- Section 3 Olfactory Threshold score

The following specific hypotheses were set out and enumerated as follows:

Section 1. Olfactory Identification and PTSD

Hypothesis I Part A.

Deficits of Olfactory Identification score at Time 1, 2 and 3 will predict a diagnosis of PTSD in trauma participants at Time 1, 2 and 3. Deficits in Olfactory Identification score will increase in those with PTSD over time. Furthermore, Olfactory Identification deficits will be greater in female PTSD than male PTSD participants.

Hypothesis I Part B.

Deficits of Olfactory Identification score at Time 1 will predict PTSD in trauma participants at Time 2 and Time 3.

Section 2. Olfactory Discrimination and PTSD

Hypothesis II Part A.

Deficits of Olfactory Discrimination score at Time 1, 2 and 3 will predict a diagnosis of PTSD in trauma participants at Time 1, 2 and 3. Deficits in Olfactory Discrimination score will increase in those with PTSD over time. Furthermore, Olfactory Discrimination deficits will be greater in female PTSD than male PTSD participants.

Hypothesis II Part B.

Deficits of Olfactory Discrimination score at Time 1 will predict PTSD in trauma participants at Time 2 and Time 3.

Section 3. Olfactory Threshold and PTSD

Hypothesis III Part A.

Deficits of Olfactory Threshold score at Time 1, 2 and 3 will predict a diagnosis of PTSD in trauma participants at Time 1, 2 and 3. Deficits in Olfactory Threshold score will increase in those with PTSD over time. Furthermore, Olfactory Threshold deficits will be greater in female PTSD than male PTSD participants.

Hypothesis III Part B.

Deficits of Olfactory Threshold score at Time 1 will predict PTSD in trauma participants at Time 2 and Time 3.

Analyses

Part A

The statistical analytical model chosen to test the hypotheses in Part A is described as follows. In order to determine whether olfactory scores predict PTSD a Generalised Estimating Equation (GEE) was fitted to the data. Generalised Estimating Equations are used to model correlated data from longitudinal repeated measures studies particularly if responses are binary (Hanley, Negassa, Edwardes and Forrester, 2003).

In this study, PTSD and olfactory measures were repeated across time on the same subjects. As it is assumed that successive measurements were correlated and thus violate the assumption of independent sampling, it was not possible to use more typical generalised linear models (such as logistic regression).

Thus, Generalised Estimating Equation (GEE) modelling (Zeger, Liang and Albert, 1988) to adjust standard errors for non-independent observations using the GENMOD procedure in SAS for personal computers version 9.2 (SAS Institute, 2002 - 2008) was

used. For release 9.2 of the SAS System, the GENMOD procedure was enhanced to support Generalised Estimating Equations, introduced by Liang and Zeger (1986) as a method of dealing with correlated data when, except for the correlation among responses, the data can be modelled with a generalised linear model. Correlated data can arise from situations such as longitudinal studies, in which multiple measurements are taken on the same participant at different points in time; and clustering, where measurements are taken on participants that share a common category or characteristic that leads to correlation. The correlation must be accounted for by analytical methods appropriate to the data. The correlated data are modelled by using the same link function and linear predictor as in a generalised linear model for the independent case. The random component by the same variance function is described. However, in the GEE approach the covariance structure of the correlated measures is modelled. The GEE method fits models to correlated data and data which do not come from a normal distribution. In this study, correlation in the data was due to repeated observations over time. These models are an extension of the classical statistical linear models but are appropriate when the responses have a distribution, which is not normally distributed or continuous.

Part B

The statistical analytical model chosen to test the hypotheses in Part B is described as follows. In order to determine whether olfactory scores at Time 1 predict PTSD at Time 2 or PTSD at Time 3 a logistic regression model was used. Logistic regression models are applied to predict the probability of occurrence of an outcome by fitting data to a logistic curve. It is a generalized linear model used for regression with a binary outcome. The fitting of these models was performed using unconditional likelihood with the LOGISTIC procedure in SAS for personal computers version 9.2 (SAS Institute, 2002 - 2008).

Logistic regression is a significant analytical technique, as the usual asymptotic methods for analyzing skewed data are unreliable. Algorithms for constructing the

required conditional distributions were introduced by Hirji, Mehta, and Patel (1987) and Mehta, Patel, and Senchaudhuri (1992, 2000). This innovation equipped these methods to become computationally available. Exact conditional inference remains valid in such situations. The LOGISTIC, procedures perform unconditional likelihood inference for logit models, and the LOGISTIC procedure can perform asymptotic conditional likelihood inference for logit models.

CHAPTER 4: RESULTS

Prevalence of PTSD

The following tables and graphs denote the prevalence of PTSD in the participants across time.

Table 1

Presence of PTSD Across Time

Time Point	No PTSD		PTSD	
	n	(%)	n	(%)
Time 1	185	(91.58)	17	(8.42)
Time 2	158	(86.33)	25	(13.66)
Time 3	142	(88.2)	19	(11.8)

As observed in Table 1, the percentage of participants with PTSD increases from Time 1 to Time 2 and moderates at Time 3.

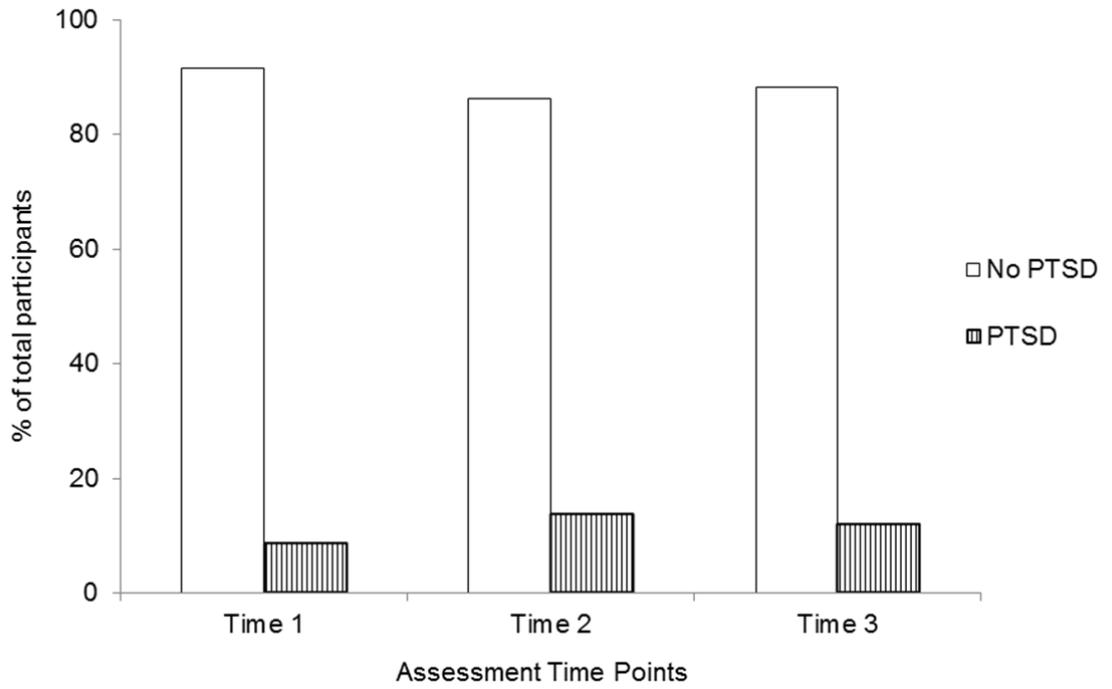


Figure 2. Percentage of No PTSD and PTSD by Time

Table 2

Presence of PTSD Across Time by Gender

Time Point	Males		Females	
	No PTSD	PTSD	No PTSD	PTSD
	n (%)	n (%)	n (%)	n (%)
Time 1	145 (92.35)	12 (7.64)	40 (88.88)	5 (12.5)
Time 2	127 (90.1)	14 (9.9)	31 (72.1)	12 (27.9)
Time 3	112 (91.0)	11 (8.94)	30 (75)	10 (25)

From Table 2 it is noted that for both males and females, the percentage of PTSD cases increases from Time 1 to Time 2 and remains high at Time 3. The relative increase in females is much higher, but the sample size is smaller.

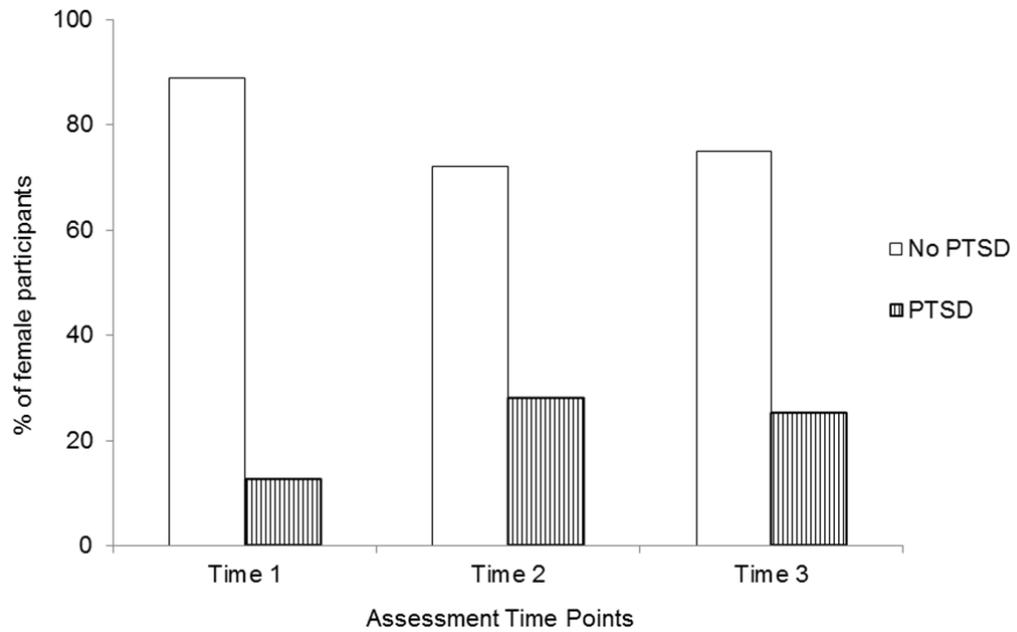


Figure 3. Percentage of No PTSD and PTSD by Time Amongst Females

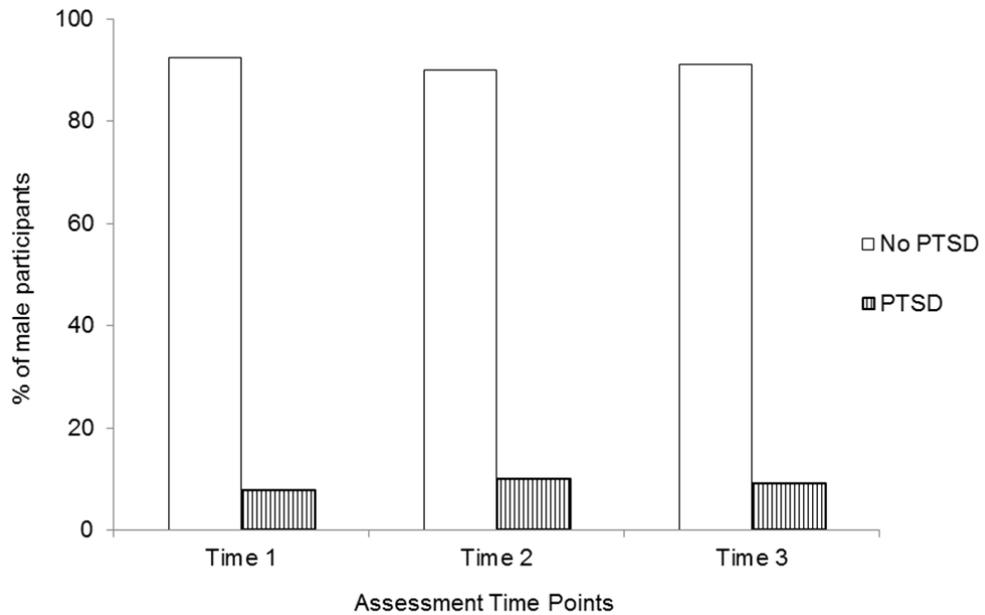


Figure 4. Percentage of No PTSD and PTSD by Time Amongst Males

Section 1. Olfactory Identification and PTSD

Hypothesis I Part A

Deficits of Olfactory Identification score at Time 1, 2 and 3 will predict a diagnosis of PTSD in trauma participants at Time 1, 2 and 3. Deficits in Olfactory Identification score will increase in those with PTSD over time. Furthermore, Olfactory Identification deficits will be greater in female PTSD than male PTSD participants.

Hypothesis I Part B

Deficits of Olfactory Identification score at Time 1 will predict PTSD in trauma participants at Time 2 and Time 3.

Descriptive Results

The following are basic frequency tables and descriptives for PTSD and Olfactory Identification scores.

Table 3

Mean Olfactory Identification Score Across Time by PTSD

Time Point	No PTSD	PTSD
	M (SD)	M (SD)
Time 1	12.29 (1.920)	11.76 (1.437)
Time 2	12.48 (1.968)	13.24 (1.128)
Time 3	12.68 (2.009)	13.58 (1.216)

Note. Mean (M), Standard Deviation (SD)

From Table 3 it is to be noted that the mean Olfactory Identification score increases for those with PTSD, while it remains relatively constant for those with no PTSD.

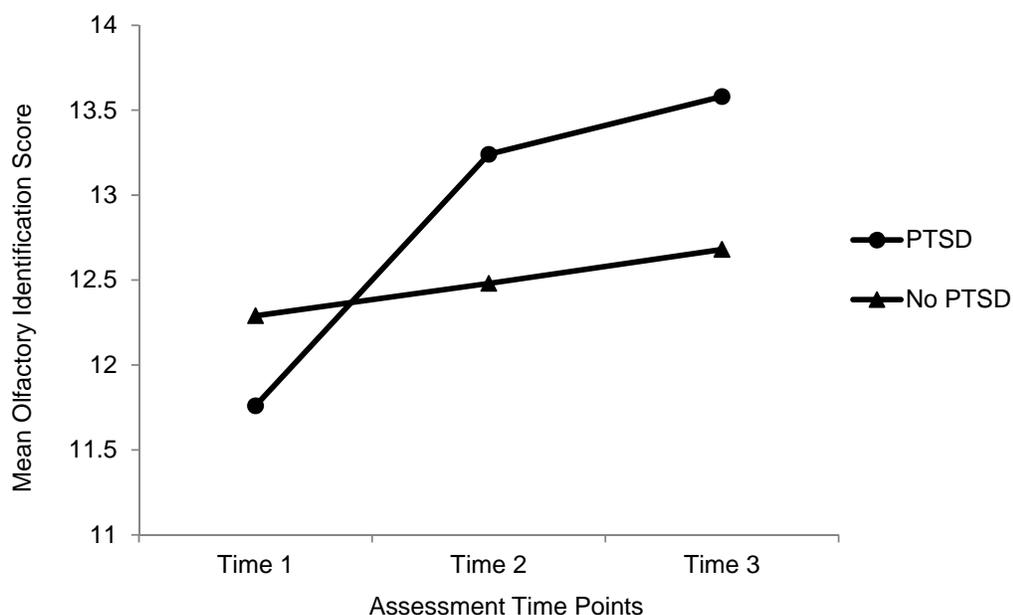


Figure 5. Mean Olfactory Identification Score for PTSD Groups by Time

Table 4

Mean Olfactory Identification Score Across Time by PTSD and Gender

Time Point	Males		Females	
	No PTSD	PTSD	No PTSD	PTSD
	M (SD)	M (SD)	M (SD)	M (SD)
Time 1	12.19 (2.001)	12.00 (1.206)	12.65 (1.562)	11.20 (1.924)
Time 2	12.43 (2.091)	12.93 (0.917)	12.68 (1.400)	13.64 (1.286)
Time 3	12.58 (2.133)	13.27 (1.272)	13.03 (1.474)	14.00 (1.069)

Note. Mean (M), Standard Deviation (SD)

From Table 4 it can be observed that in regards to Identification score, females show a higher score. Within both males and females, those with PTSD show a slightly lower score at Time 1 however, the Identification score increases at Times 2 and 3.

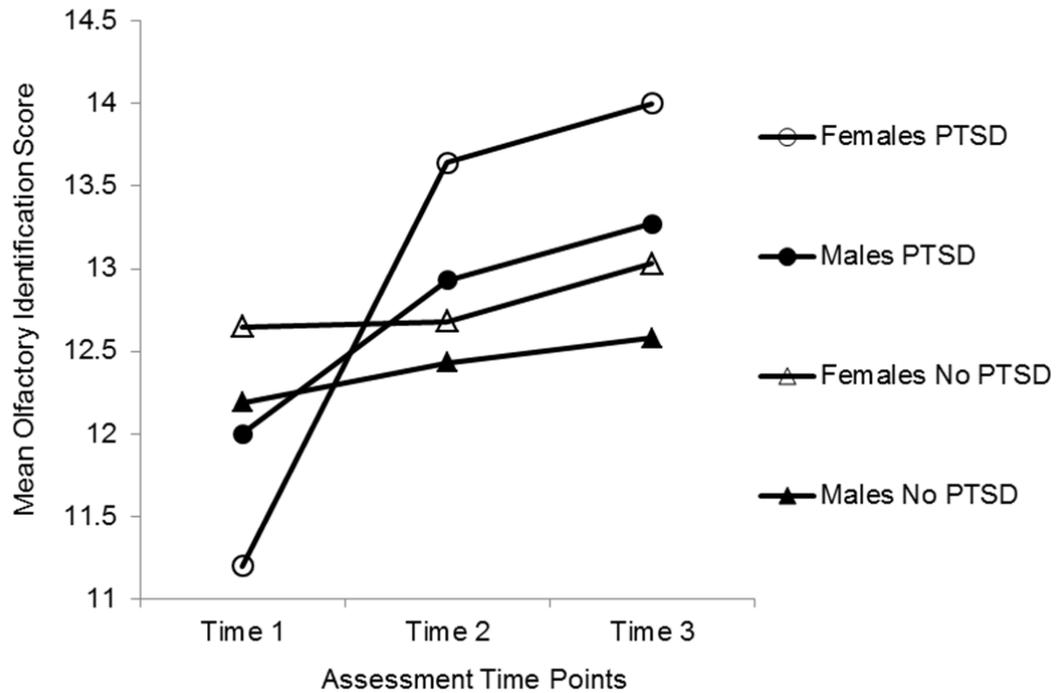


Figure 6. Mean Olfactory Identification Score at Each Time Point for PTSD Groups by Gender

Hypothesis I Part A: Analysis of Olfactory Identification Score by PTSD

Results

To test whether there was an Olfactory Identification score interaction by PTSD over time and whether this was qualified by gender, the following analyses were conducted. A binomial GEE with logit link model was used in order to further determine the relationship between Olfactory Identification score, PTSD and gender over time.

Following this the three way interaction between time Olfactory Identification score and

gender was removed as it was not significant and gender was left as a main effect, and the Identification score by time interaction assessed. Comparisons of low and high Identification scores at each time point were then obtained, and comparisons of the time point within high and low values of Identification score were also obtained. Low and high values of Identification score were defined as 10 and 14, respectively (roughly 1 SD below and above the mean score).

The first analysis conducted was between Olfactory Identification score, Gender and Time.

GEE results.

Table 5

Olfactory Identification Score, Gender and Time Analysis

Source	DF	Chi-Square	Pr > ChiSq
ID Score	1	2.31	0.1286
Time	2	6.72	0.0348
ID Score*Time	2	7.66	0.0218
GENDER	1	0.14	0.7131
ID Score*GENDER	1	0.34	0.5613

Source	DF	Chi-Square	Pr > ChiSq
Time*GENDER	2	4.36	0.1132
ID Score*Time*Gender	2	4.81	0.0904

Note. Olfactory Identification Score (ID), Degrees of Freedom (DF)

Score Statistics for Type 3 GEE Analysis

From Table 5 the model with the three-way Identification Score*Gender*Time interaction shows that the interaction is not significant. This indicates that the influence of Identification score on PTSD status over time is not different for males and females.

Table 6

Olfactory Identification Score and Time Analysis

Source	DF	Chi-Square	Pr > ChiSq
ID Score	1	3.46	0.0629
Time	2	7.60	0.0224
ID Score*Time	2	8.90	0.0117
Gender	1	4.30	0.0381

Note. Olfactory Identification Score (ID), Degrees of Freedom (DF),

Score Statistics for Type 3 GEE Analysis

As can be noted from Table 6 when Gender remains as a main effect, the Identification Score*Time interaction is significant (chi-square, 2df = 8.90, p = 0.0117) indicating that the influence of Identification score on PTSD does change across the time

points. There is also a main effect of Gender indicating that overall, there is a difference in PTSD status based on Gender (chi-square, 1 df=4.30, $p = 0.0381$).

In order to ascertain whether Identification score and Gender predicts PTSD status over time the following GEE analysis was conducted with PTSD as the variable and Gender as the main effect.

Table 7

Parameter Estimates for Predicting PTSD Status from Olfactory Identification Score, Gender and Time

Source	Estimate	SE	Z	p
Intercept	-5.4635	1.9077	-2.86	0.0042
ID Score	0.3073	0.1429	2.15	0.0315
Time 1	5.5639	2.1538	2.58	0.0098
Time 2	0.9978	1.9937	0.50	0.6167
Time 3	0.0000	0.0000		
ID Score*Time 1	-0.4622	0.1653	-2.80	0.0052
ID Score*Time 2	-0.0565	0.1505	-0.38	0.7073
ID Score*Time 3	0.0000	0.0000		
GENDER (male)	-0.8738	0.3654	-2.39	0.0168
GENDER (female)	0.0000	0.0000		

Note. Olfactory Identification Score (ID), Standard Error (SE)

Table 8

Planned Comparisons of Olfactory Identification Score

Comparison	OR	(95%) CI	Chi-Square	p
High vs Low				
Time 1 (T1)	0.5382	(0.2610 - 1.1095)	2.82	0.0933
Time 2 (T2)	2.7270	(1.1913 - 6.2426)	5.64	0.0176
Time 3 (T3)	3.4189	(1.1154 - 10.479)	4.63	0.0315
At Low Levels of ID Score				
Change: T1 to T2	0.6010	(0.2623 - 1.3771)	1.45	0.229
Change: T2 to T3	0.6488	(0.2312 - 1.8209)	0.68	0.411
Change: T1 to T3	0.3900	(0.1255 - 1.2120)	2.65	0.104
At High levels of ID Score				
Change: T1 to T2	3.0455	(1.4279 - 6.4956)	8.30	0.004
Change: T2 to T3	0.8135	(0.4898 - 1.3509)	0.64	0.425
Change: T1 to T3	2.4774	(1.1776 - 5.2121)	5.72	0.017
Gender				
Females vs Males	2.3960	(1.1707 - 4.9034)	5.72	0.017

Note. Olfactory Identification Score (ID), Odds Ratio (OR), Confidence Interval (CI)

Comparisons of low and high Olfactory Identification scores at each time point were obtained, and comparisons of the time point within high and low values of Identification score were also obtained. Low and high values of Identification score were

defined as 10 and 14, respectively (approximately 1 SD below and above the mean score). Thus for participants with either a low or high Olfactory Identification score the odds ratio (OR) of a diagnosis of PTSD was determined across time by using a planned comparison in the GEE.

From the contrast estimate results in Table 8 the following conclusions can be made of Olfactory Identification comparisons at each of the three time points:

- Firstly at Time 1 participants with low Olfactory Identification scores are more likely than those with high scores to have ASD, though this is not significant (OR = 0.538, chi-square = 2.82, $p = 0.093$).
- However at Time 2 participants with high Olfactory Identification scores are significantly more likely than those with low scores to show PTSD (OR = 2.727, chi-square = 5.64, $p = 0.018$). The odds of a participant with a high Olfactory Identification score having PTSD are almost 3 times that of a low score participant.
- Furthermore at Time 3, participants with high Olfactory Identification scores are significantly more likely than those with low scores to show PTSD (OR = 3.419, chi-square = 4.63, $p = 0.032$). The odds of a participant with a high Olfactory Identification score having PTSD is 3.4 times that of a low score person.

When comparing changes across Time for participants with low and high Olfactory Identification scores, the following conclusions can be made:

Participants with Low Olfactory Identification scores.

- For a low scorer, the change in odds of PTSD at Time 2 relative to Time 1 is not significant (OR = 0.601, chi-square = 1.45, $p = 0.289$).
- For a low scorer, the change in odds of PTSD at Time 3 relative to Time 2 is not significant (OR = 0.649, chi-square = 0.30, $p = 0.411$).

- For a low scorer, the change in odds of PTSD at Time 3 relative to Time 1 is not significant (OR = 0.390, chi-square = 2.65, $p = 0.104$).

Participants with High Olfactory Identification scores.

- For a High scorer, the change in odds of PTSD at Time 2 relative to Time 1 is significant (OR = 3.046, chi-square = 8.30, $p = 0.004$). Therefore, for a participant with a high Olfactory Identification score, the odds of a PTSD diagnosis at Time 2 are 3 times as high as at Time 1.
- For a High scorer, the change in odds of PTSD at Time 3 relative to Time 2 is not significant (OR = 0.814, chi-square = 0.64, $p = 0.425$).
- For a High scorer, the change in odds of PTSD at Time 3 relative to Time 1 is significant (OR = 2.447, chi-square = 5.72, $p = 0.017$). Thus for a participant with a high Identification score, the odds of a PTSD diagnosis at Time 3 are approximately 2.5 times as high as at Time 1.

The odds of a female showing PTSD are 2.396 times as high as for a male (chi-square = 5.72, $p = 0.0168$).

Part A: Conclusion.

The influence of Olfactory Identification score on odds of PTSD diagnosis does change over time. At Time 1, there was no difference in the odds of PTSD diagnosis between those with low and high scores. However, at Time 2 the odds of PTSD diagnosis for those with high scores increased 3 fold over those with low scores. This difference remained at Time 3.

The pattern of change over time differed for the high and low groups as well. There was no significant change in odds of PTSD diagnosis across time for those with low Olfactory Identification scores. For those with high Olfactory Identification scores, the

odds of diagnosis increased 3 fold from Time 1 to Time 2, and remained elevated at Time 3.

Hypothesis 1 Part B: Analysis of Olfactory Identification Score at Time 1 Predicting PTSD at Time 2 or Time 3

In order to investigate whether Olfactory Identification score at Time 1 predicts PTSD at Time 2 or Time 3 logistic regression models were applied. Results indicated that there was no relationship between Olfactory Identification score at Time 1 and a diagnosis of PTSD at Time 2 or PTSD at Time 3.

Part B: Conclusion.

Olfactory Identification score at Time 1 is not predictive of PTSD at Time 2 or Time 3.

Section 2. Olfactory Discrimination Score and PTSD

Hypothesis II Part A

Deficits of Olfactory Discrimination score at Time 1, 2 and 3 will predict a diagnosis of PTSD in trauma participants at Time 1, 2 and 3. Deficits in Olfactory Discrimination score will increase in those with PTSD over time. Furthermore, Olfactory Discrimination deficits will be greater in female PTSD than male PTSD participants.

Hypothesis II Part B

Deficits of Olfactory Discrimination score at Time 1 will predict PTSD in trauma participants at Time 2 and Time 3.

Descriptive Results

The following are basic frequencies and descriptives for PTSD and Olfactory Discrimination score.

Table 9

Mean Olfactory Discrimination Score Across Time by PTSD

Time Point	No PTSD	PTSD
	M (SD)	M (SD)
Time 1	10.88 (2.432)	11.53 (2.004)
Time 2	11.37 (2.322)	11.44 (2.755)
Time 3	11.78 (2.471)	11.84 (2.566)

Note. Mean (M), Standard Deviation (SD)

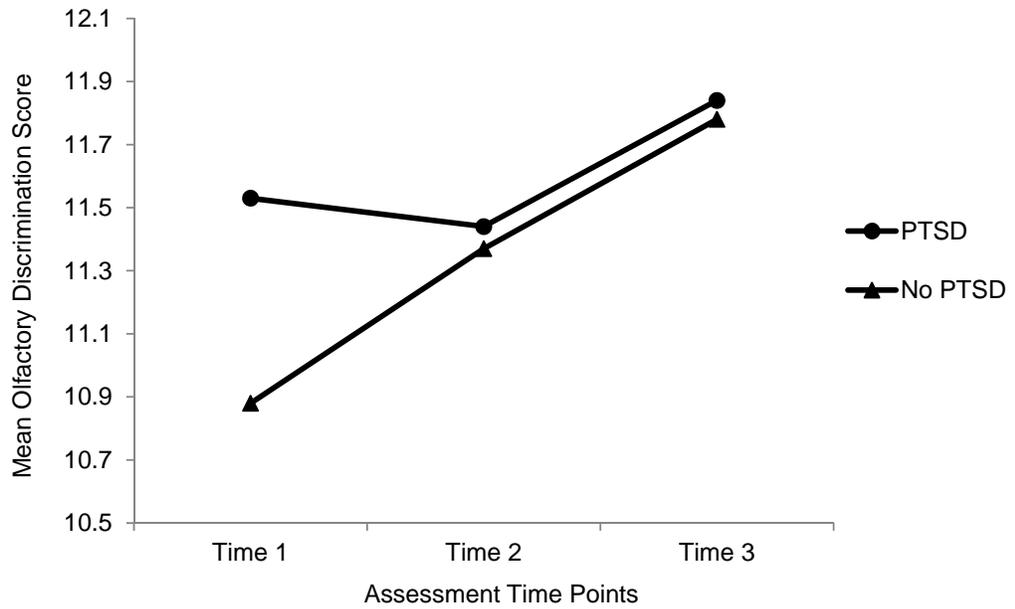


Figure 7. Mean Discrimination Score for PTSD Groups by Time

Table 10

Mean Olfactory Discrimination Score Across Time by PTSD and Gender

	Males		Females	
	No PTSD	PTSD	No PTSD	PTSD
	M (SD)	M (SD)	M (SD)	M (SD)
Time 1	10.74 (2.356)	11.33 (2.146)	11.35 (2.666)	12.00 (1.732)
Time 2	11.20 (2.356)	10.64 (2.977)	12.00 (2.113)	12.45 (2.162)
Time 3	11.53 (2.588)	10.73 (2.494)	12.67 (1.768)	13.38 (1.847)

Note. Mean (M), Standard Deviation (SD)

From Table 10 it can be ascertained that females tend to show higher Discrimination scores overall and both males and females showed increases over time in Discrimination score.

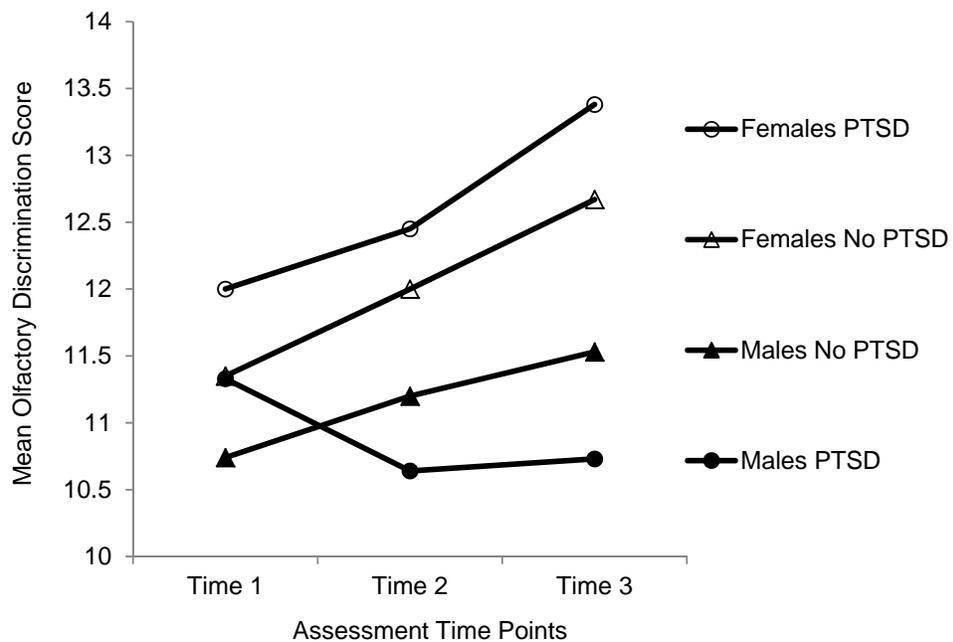


Figure 8. Mean Discrimination Score at Each Time Point for PTSD Groups

Hypothesis II Part A: Analysis of Olfactory Discrimination score by PTSD Results

In order to test whether there was an Olfactory Discrimination score interaction by PTSD over time several type 3 GEE Analyses were conducted.

The first analysis conducted was between Time and Olfactory Discrimination score. The second analysis was conducted to determine whether the relationship between Olfactory Discrimination and PTSD status is affected by gender.

As PTSD is a dichotomous variable and there are repeated measurements, generalised estimating equations (GEE) were used to estimate the influence of Identification score on presence of PTSD symptoms over time. Thus, the model determines whether Olfactory Discrimination score influences the presence of PTSD over time and is this qualified by gender.

(Technical information about the model) A binomial GEE with logit link was used to examine the relationship between Discrimination score and PTSD over time (first model). Then, gender was added as a factor and the three way interaction between Discrimination, time and gender was assessed. Because the three-way interaction with gender was not significant, a final model was run with gender as a main effect only. Because there were no effects of Discrimination on PTSD, nor was there a Discrimination score by time interaction, no estimates from the model were produced.

GEE results.

In the model with Olfactory Discrimination and Time only, there were no significant effects. Thus Discrimination score does not predict PTSD status over time.

By adding gender to the model, the following tables were generated:

Table 11

Olfactory Discrimination Score, Gender and Time Analysis

Source	DF	Chi-Square	Pr > ChiSq
Discrimination Score	1	0.82	0.3653
Time	2	0.76	0.6823
Discrimination Score*Time	2	0.41	0.8145
GENDER	1	0.65	0.4184
Discrimination Score*GENDER	1	1.71	0.1908
Time*GENDER	2	0.89	0.6393
Discrimination*Time*GENDER	2	1.11	0.5736

Note. Degrees of Freedom (DF), Score Statistics for Type 3 GEE Analysis

From Table 11 the model with the three-way Olfactory Discrimination Score*Gender*Time interaction showed that the three way interaction is not significant. This indicates that the influence of Identification score on PTSD status over time is not different for males and females.

Table 12

Olfactory Discrimination Score and Time Analysis

Source	DF	Chi-Square	Pr > ChiSq
Discrimination Score	1	0.07	0.7972
Time	2	1.53	0.4665
Discrimination Score*Time	2	0.97	0.6158
GENDER	1	4.63	0.0314

Note. Degrees of Freedom (DF), Score Statistics for Type 3 GEE Analysis

From Table 12 it is noted that the main effect of gender was significant (chi-square, 1df=4.63, $p = 0.0314$). Thus, it can be stated that females perform the Olfactory Discrimination task significantly better than males.

Part A: Conclusion.

From the analysis and as indicated in Table 11 and Table 12 the following conclusions can be made of Olfactory Discrimination comparisons at each of the three time points:

- There is no influence of Discrimination score on PTSD status over time and it is not different for males and females.
- Females significantly outperform males on the Discrimination task.

Hypothesis II Part B: Analysis of Olfactory Discrimination score at Time 1 predicting PTSD at Time 2 and 3

Part B: Conclusion.

In order to investigate whether Olfactory Discrimination score at Time 1 predicts PTSD at Time 2 or Time 3 logistic regression models were applied. Results indicated that

there was no relationship between Olfactory Discrimination score at Time 1 and a diagnosis of PTSD at time 2 or PTSD at time 3.

Section 3. Olfactory Threshold Score and PTSD

Hypothesis III Part A

Deficits of Olfactory Threshold score at Time 1, 2 and 3 will predict a diagnosis of PTSD in trauma participants at Time 1, 2 and 3. Deficits in Olfactory Threshold score will increase in those with PTSD over time. Furthermore, Olfactory Threshold deficits will be greater in female PTSD than male PTSD participants.

Hypothesis III Part B

Deficits of Olfactory Threshold score at Time 1 will predict PTSD in trauma participants at Time 2 and Time 3.

Descriptive Results

The following are basic frequency tables and descriptives for PTSD and Olfactory Threshold scores.

Table 13

Mean Olfactory Threshold Score Across Time by PTSD and Gender

	Males		Females	
	No PTSD	PTSD	No PTSD	PTSD
	M (SD)	M (SD)	M (SD)	M (SD)
Time 1	7.250 (2.542)	7.229 (3.554)	8.679 (2.746)	9.950 (3.407)
Time 2	7.478 (2.751)	8.000 (2.260)	9.331 (2.641)	10.50 (3.541)
Time 3	8.162 (2.858)	7.659 (2.508)	8.658 (2.977)	12.47 (2.782)

Note. Mean (M), Standard Deviation (SD)

From Table 13 it can be noted that for Threshold scores, females with PTSD show a markedly higher mean Threshold score than females without PTSD and males, regardless of PTSD status.

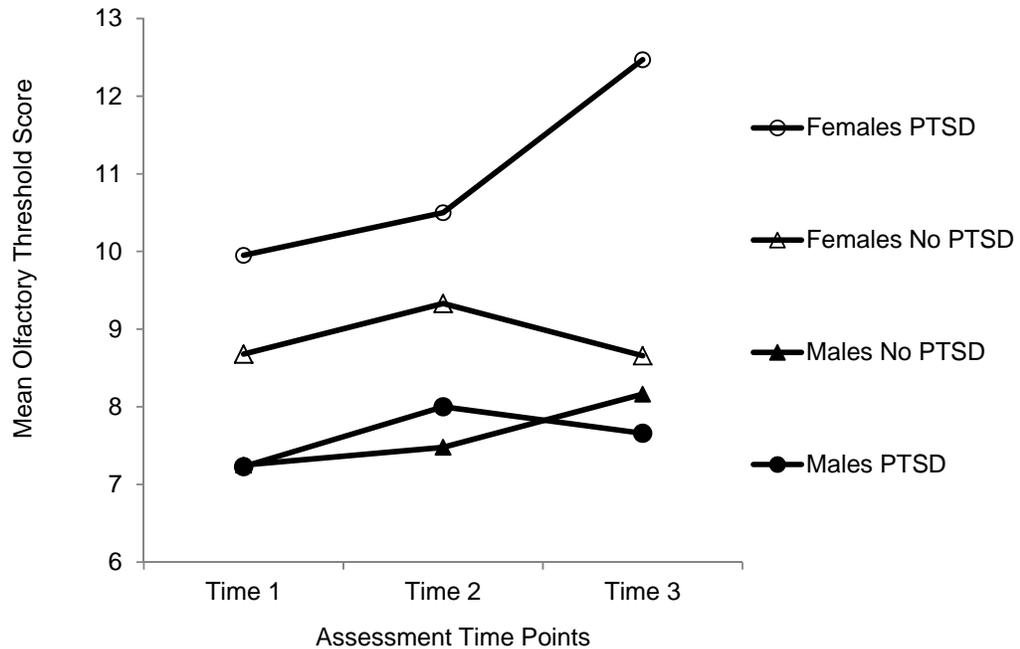


Figure 9. Mean Threshold Score at Each Time Point for PTSD Groups by Gender

Hypothesis III Part A: Analysis of Olfactory Threshold Score by PTSD Results

The following analyses were conducted to determine the influence of Olfactory Threshold score on PTSD changes over time and whether it is qualified by gender.

As PTSD is a dichotomous variable and there are repeated measurements, generalised estimating equations (GEE) were used to estimate the influence of Threshold score on presence of PTSD symptoms over time. A binomial GEE with logit link was used to examine the relationship between Threshold score, PTSD and gender over time.

GEE results.

First, a model with the three-way interaction between Threshold score, gender and time was run:

Table 14

Olfactory Threshold Score, Gender and Time Analysis

Source	DF	Chi-Square	Pr > ChiSq
Threshold Score	1	4.77	0.0289
Time	2	1.47	0.4788
Threshold Score*Time	2	1.30	0.5212
GENDER	1	2.61	0.1065
Threshold Score *GENDER	1	4.66	0.0309
Time*GENDER	2	2.84	0.2418
Threshold Score *Time*GENDER	2	3.15	0.2075

Note. Degrees of Freedom (DF), Score Statistics for Type 3 GEE Analysis

From Table 14 it can be noted that the three-way Olfactory Threshold score by gender by time interaction is not significant. This indicates that the influence of Threshold score on PTSD status over time is not different for males and females. Then, the interaction was removed (it was not significant).

Table 15

Olfactory Threshold Score and Gender Analysis

Source	DF	Chi-Square	Pr > ChiSq
Threshold Score	1	4.41	0.0357
Time	2	0.16	0.9240
Threshold Score*Time	2	0.26	0.8776
GENDER	1	1.90	0.1677
Threshold Score*GENDER	1	4.50	0.0339
Time*GENDER	2	0.35	0.8376

Note. Degrees of Freedom (DF), Score Statistics for Type 3 GEE Analysis

When two-way interactions are included in the model, the gender by Threshold score was significant. This indicates that the influence of Threshold score on PTSD status is different for males and females. Because the interaction between Threshold score and gender was significant, the two-way interactions in the model were retained.

Comparisons of low and high Threshold scores within gender and gender differences at high and low Threshold scores were obtained. Low and high values of Threshold score were defined as 5 and 10, respectively (roughly 1 SD below and above the mean score).

In order to ascertain how the interaction is working, comparisons of high and low Threshold score within females and within males were obtained. In addition, within high and low scores, comparisons of males and females were obtained.

Table 16

Parameter Estimates for Predicting PTSD Status from Olfactory Threshold Score, Gender and Time

Source	Estimate	SE	Z	p
Intercept	-4.3158	1.3019	-3.31	0.0009
Threshold Score	0.2915	0.1128	2.58	0.0098
Time 1	0.1467	1.3916	0.11	0.9160
Time 2	0.6388	1.5061	0.42	0.6714
Time 3	0.0000	0.0000	.	.
Threshold Score*Time 1	-0.0685	0.1331	-0.51	0.6066
Threshold Score*Time 2	-0.0304	0.1298	-0.23	0.8152
Threshold Score*Time 3	0.0000	0.0000	.	.
GENDER 1	1.6758	1.4159	1.18	0.2366
GENDER 2	0.0000	0.0000	.	.
Threshold Score*GENDER 1	-0.2538	0.1282	-1.98	0.0477
Threshold Score*GENDER 2	0.0000	0.0000	.	.
Time 1*GENDER 1	0.2293	0.7132	0.32	0.7478
Time 1*GENDER 2	0.0000	0.0000	.	.
Time 2*GENDER 1	-0.2594	0.6234	-0.42	0.6774
Time 2*GENDER 2	0.0000	0.0000	.	.
Time 3*GENDER 1	0.0000	0.0000	.	.
Time 3*GENDER 2	0.0000	0.0000	.	.

Note. Standard Error (SE)

Table 17

Planned Comparisons of Olfactory Threshold Scores (High vs Low & Gender)

Comparison	OR	(95%) CI	Chi-Square	p
High Vs Low				
Female	3.6424	(1.2799 - 10.3656)	5.87	0.0154
Males	1.0239	(0.5010 - 2.0929)	0.00	0.9483
Females vs Males				
Low	0.6725	(0.1469 - 3.0777)	0.26	0.6091
High	2.3922	(1.0291 - 5.5607)	4.11	0.0427

Note. Odds Ratio (OR)

From Table 17 we note that:

- Amongst females, those with high Threshold scores were 3.64 times as likely to show PTSD as females with low scores (chi-square = 5.87, p = 0.015) across the three time spans.
- Amongst males, there was no significant difference in odds of PTSD between those with high and low Threshold scores (odds ratio = 1.02, chi-square = 0.00, p = 0.948).
- For those with low Threshold score, there was no significant difference in odds of PTSD between males and females (odds ratio = 0.673, chi-square = 0.26, p = 0.609).
- Among those with high Threshold scores, females were 2.39 times as likely to show PTSD as males with high Threshold scores (chi-square = 4.11, p = 0.043) across the three time spans.

PartA: Conclusion.

As noted from Tables 14,15,16 and17 the most noticeable risk factors for PTSD are amongst females with high Olfactory Threshold scores across time spans. Note also that following diagnosis of PTSD female Olfactory Threshold scores continue to escalate (Figure 8).

Hypothesis III Part B: Analysis of Olfactory Threshold Score at Time 1 Predicting PTSD at Time 2 and 3

In order to investigate whether Olfactory Threshold score at Time 1 predicts PTSD at Time 2 or Time 3 logistic regression models were applied.

Logistic regression results: Time 1 predicting PTSD at Time 2.

First, a univariate model between Threshold score at Time 1 and PTSD at Time 2 was run.

Table 18

Parameter Estimates for Predicting PTSD Status at Time 2 from Olfactory Threshold Score at Time 1

Parameter	Estimate	SE	Wald Chi-Square	Pr > ChiSq
Intercept	-3.2274	0.7271	19.70	<.0001
Threshold Score at Time 1	0.1613	0.0822	3.85	0.0496

Note. Standard Error (SE)

From Table 18 it is noted that there is a relationship between Olfactory Threshold score at Time 1 and a diagnosis of PTSD at Time 2.

Table 19

Planned Comparison of High vs Low Olfactory Threshold Scores at Time 1 to Predict PTSD at Time 2

Comparison	OR	(95%) CI	Chi-Square	p
High vs Low	2.2396	(1.0012 – 5.0097)	3.85	0.0496

Note. Odds Ratio (OR), Confidence Interval (CI)

From Table 19 we note that:

- Participants with high Threshold scores at Time 1 were 2.24 times as likely to show PTSD at Time 2 as participants with low Threshold scores at Time 1 (chi-square = 3.85, p = 0.0496).

Logistic regression results: Time 1 predicting PTSD at Time 3.

Secondly, a univariate model between Threshold score at Time 1 and PTSD at Time 3 was run. There was no significant relationship. However in order to test for an interaction between Threshold scores at Time 1 and gender predicting PTSD at Time 3 the following multivariate logistic regression was run.

Table 20

Parameter Estimates for Predicting PTSD Status at Time 3 from Olfactory Threshold Score at Time 1 by Gender.

Parameter	Estimate	SE	Wald Chi-Square	Pr > ChiSq
Intercept	-1.5325	0.9008	2.89	0.0889
Threshold Score at Time 1	-0.1162	0.1284	0.82	0.3653
Gender	-3.3882	2.0511	2.73	0.0986
Threshold Score*Gender	0.4865	0.2202	4.88	0.0272

Note. Standard Error (SE)

From Table 20 it is noted that there is a relationship between Olfactory Threshold score at Time 1 and a diagnosis of PTSD at Time 3 by Gender.

Table 21

Planned Comparison of Olfactory Threshold Scores (High vs Low & Gender) at Time 1 to Predict PTSD at Time 3

Comparison	OR	(95%) CI	Chi-Square	p
High vs Low	1.8873	(0.6415 – 5.5527)	1.33	0.2487
Female vs Male	0.0338	(0.0006 – 1.8811)	2.73	0.0986
High Vs Low				
Males	0.5592	(0.1589 – 1.9679)	0.82	0.3653
Females	6.3693	(1.1028 – 36.785)	4.28	0.0385
Females vs Males				
Low	0.3846	(0.0474 - 3.1223)	0.80	0.3712
High	4.3805	(1.0935 - 17.548)	4.35	0.0370

Note. Odds Ratio (OR), Confidence Interval (CI)

From Table 21 we note that:

- Female participants with high Threshold scores at Time 1 were 6.4 times as likely to show PTSD at Time 3 than female participants with low Threshold scores at Time 1 (chi-square = 4.28, p = 0.0385).
- Among those with high Threshold scores at time 1, females were 4.4 times as likely to show PTSD at Time 3 than males (chi-square = 4.35, p = 0.0370).

Part B: Conclusion.

As Tables 18, 19, 20 and 21 demonstrate, initial high Olfactory Threshold scores significantly predict PTSD for both males and females at Time 2 and for females at Time

3

CHAPTER 5: DISCUSSION

Background

Prior to the current investigation, three studies had been reported specifically examining PTSD and olfaction. Two studies tested Vietnam veterans and found Olfactory Identification deficits in veterans with PTSD in contrast to veterans without PTSD. The authors in both studies concluded that this was due to an element of the underlying pathophysiology of PTSD, possibly OFC dysfunction (Dileo, Brewer, Hopwood, Anderson and Creamer, 2008; Vasterling, Brailey and Sutker, 2000). In contrast, the other exploratory study by Croy, Schellong, Joraschky and Hummel (2010) obtained results of enhanced Odour Identification in those with PTSD and no difference in Threshold levels. The authors proposed that as Olfactory Identification reflects central processing then enhanced orbitofrontal functioning may explain this result. These contrasting results and conclusions indicated that further research is required to clarify the relationship between PTSD and olfaction.

This research exists against the background of a significant body of literature demonstrating olfactory dysfunction in those suffering from various neurological and psychiatric disorders (Doty, 1994; Barresi, Ciurleo, Giacoppo, Foti Cuzzola, Celi, Bramanti and Marino, 2012). Most of the studies have been in the domain of Olfactory Identification but Threshold is also affected in some disorders. Olfactory Identification deficits have been unequivocally demonstrated in those with disorders such as schizophrenia, Parkinson's disease, Huntington's Chorea, Alzheimer's and Multiple Sclerosis to name a few. Other psychiatric disorders have also been investigated and various olfactory dysfunctions have been evident in these disorders.

Although Olfactory Identification deficits are observed in those with neurological disorders, a significant characteristic less recognised is the phenomenon of deficits being

observed prior to any overt neurological symptoms. This characteristic is evident in those with Parkinson's, schizophrenia, Alzheimer's and multiple sclerosis. Olfactory Identification deficits are also noticed in first-degree relatives of those with these disorders who themselves do not have the disorder, indicating a genetic component to the vulnerability (Turetsky, Kohler, Gur and Moberg, 2008; Siderowf, Jennings, Connolly, Doty, Marek and Stern, 2007). Thus, the finding that Olfactory Identification deficits predate the onset of neurological disorders has significant ramifications. For instance those who have a family history of Alzheimer's, schizophrenia or Parkinson's and have a lower than expected Olfactory Identification score may be particularly vulnerable to that disorder. A longitudinal study examining the relationship between olfaction and individuals deemed at high risk for psychosis found that those with Olfactory Identification deficits were more likely to develop schizophrenia later (Brewer, Wood, McGorry, Francey, Phillips, Yung, Anderson, Copolov, Singh, Velakoulis and Pantelis, 2003). This result and subsequent studies have concluded that olfactory deficits are currently one of the most predictive biomarkers of psychosis (Turetsky, Kamath, Calkins, Brewer, Wood, Pantelis, Seidman, Malaspina, Good, Kopala and Moberg, 2012).

Thus, these findings lead to the conclusion that testing olfactory function may be a useful screening tool to determine biological vulnerability to particular neurological and psychiatric disorders. This project aimed to explore the relevance of this body of work to the investigation of PTSD. To date no studies have been conducted to determine whether olfactory deficits predate the onset of PTSD. However based on the outcome of other longitudinal studies, which have examined olfactory precursors to neurological disorders, it was hypothesised that this may be the case. Given that there is such a considerable overlap of the olfactory and limbic systems, one may hypothesise that dysfunction in one system would be manifest in the other. Thus, an individual with a compromised or vulnerable

limbic system may present with concomitant olfactory deficits. Such an individual may be predisposed to develop PTSD after trauma due to a pre-existing biological vulnerability.

Therefore, the purpose of the study was to determine whether olfactory deficits predate the onset of PTSD in trauma survivors.

There have been two previous studies noting a relationship between Olfactory Identification and PTSD. These were conducted by Vasterling, Brailey and Sutker (2000) and Dileo, Brewer, Hopwood, Anderson and Creamer (2008). Both studies examined Vietnam veterans. Amongst the veterans were those who had trauma exposure and did not have PTSD, those who had trauma exposure and did have PTSD and those who had no trauma exposure and no PTSD. The results indicated that those with PTSD had Olfactory Identification deficits in contrast to those who did not have PTSD. The results of these studies instigated a series of questions, which this research addressed.

Firstly, does low Olfactory Identification predict PTSD? This question was examined by testing olfaction in the immediate post trauma period when PTSD cannot be diagnosed, as the symptoms must be present for a month to satisfy the diagnostic criteria. The latency period before a series of neurobiological dysregulation emerge has been shown with phenomena that have a well characterised physiology such as the startle response (Shalev, Peri, Brandes, Freedman, Orr and Pitman, 2000). Thus, low Olfactory Identification in trauma survivors with PTSD may reflect a pre-existing risk marker.

Secondly, if low Olfactory Identification does not predict PTSD, does PTSD precipitate Olfactory Identification deficits and when is the deficit likely to manifest? This question was posed because of an alternative hypothesis that the olfactory deficits in PTSD are a consequence of the neurobiology of the disorder rather than a risk marker. For instance, an identical twin study noted amplified heart rates to sudden loud tones, which is a developed response in those with PTSD (Pitman, Gilbertson, Gurvits, May, Lasko, Metzger, Shenton, Yehuda and Orr, 2006).

Thirdly, is there a relationship between PTSD and low Olfactory Threshold and low Olfactory Discrimination? This question was posed as to date there has not been any research conducted on whether there is a relationship between PTSD and other elements of olfactory functioning. Thus, this research is a first in this regard.

Significant Results

From the outset it must be stated that the following significant results were most unexpected, were the antithesis of what was hypothesised, are difficult to explain and raise many questions.

Summary Statement of the Major Findings

The results do not support the research hypothesis that:

- Low olfactory functioning (Threshold, Identification and Discrimination) predicts PTSD or is related to PTSD within the first year.
- The results contradict the research hypothesis and suggest that:

Threshold.

- High Olfactory Threshold at Time 1 (Time of admission) is a predictive measure of PTSD at Time 2 (3 months) for both males and females, i.e., those more sensitive as indicated by high Threshold were more likely to develop PTSD.
- High Olfactory Threshold at Time 1, is a predictive measure of PTSD at Time 3 (12 months) for females.
- Female participants with high Threshold scores at Time 1 were 6.4 times more likely to show PTSD at Time 3 than female participants with low Threshold scores at Time 1.
- Female participants with high Threshold scores (in comparison to low Threshold scores) are 3.64 times more likely to show PTSD across the three time intervals (Time 1, Time 2 and Time 3).

- Among those with high Threshold scores, females were 2.4 times as likely to show PTSD as males with high Threshold scores across the three time intervals (Time 1, Time 2 and Time 3).
- Among those with high Threshold scores at Time 1, females were 4.4 times more likely to show PTSD at Time 3 than males.
- In summary, females in particular are more prone to PTSD if they have a high Olfactory Threshold but this relationship also existed for males at 3 months.

Identification.

- High Olfactory Identification scores (in comparison to low Identification scores) are significantly related to PTSD at Time 2 and 3.
- Across the time intervals, the odds of PTSD diagnosis for those with high Olfactory Identification scores increased threefold from Time 1 to Time 2, and remained elevated at Time 3.
- In summary, these findings suggest that those individuals who are good at qualifying the smells in their environment are more at risk of conditioning and sensitisation to olfactory triggers in their environment. The result also confirms the findings of Croy, Schellong, Joraschky and Hummel (2010).

These findings will now be described and discussed in more detail.

Olfactory Threshold.

The most notable results of the study were the relationships between PTSD and Olfactory Threshold. To date there is no literature associating Olfactory Threshold and PTSD, so these findings are a first in this regard.

Firstly, high Olfactory Threshold was a predictive measure of PTSD. A high Olfactory Threshold score at Time 1 predicted PTSD for both males and females at Time 2. Specifically, at Time 1 participants with high Threshold scores (in comparison to those

with low Threshold scores) were 2.24 times more likely to have PTSD at Time 2. In addition, amongst females, a high Olfactory Threshold score at Time 1 predicted PTSD at Time 3. Specifically females with high Threshold scores at Time 1 were 6.4 times more likely to have PTSD at Time 3 than females with low Threshold scores at Time 1. Amongst male and female participants with high Threshold scores at Time 1, female participants were 4.4 times more likely to have PTSD than male participants at Time 3. These results indicate several dynamic interactions with PTSD. Not only was Threshold a predictive measure of PTSD but also the relationship was found to be dynamic across gender and time.

As the influence of Threshold score on PTSD status is different for males and females over time, comparisons of high and low Threshold scores within females and within males were obtained. In addition, within high and low Threshold scores, comparisons of males and females were obtained. A comparison of change in odds of PTSD diagnosis across time amongst female participants indicated that those with high Olfactory Threshold scores were 3.64 times as likely to show PTSD as females with low scores across the three time intervals. Conversely, amongst males, there was no significant difference in odds of PTSD between those with high and low Threshold scores. Further comparisons of change in odds of PTSD diagnosis across time indicated that amongst those with high Threshold scores females were 2.39 times as likely to show PTSD as males across the three time intervals. Conversely, for those with low Threshold score, there was no significant difference in odds of PTSD between males and females.

These results were significantly contrary to what was hypothesised. It was hypothesised that low Olfactory Threshold scores would predict PTSD and that these scores would deteriorate across time amongst those with PTSD. The reason for this was the view that Olfactory Threshold scores would most likely follow a similar trajectory to

the previous findings of low Olfactory Identification and PTSD as noted by Dileo, Brewer, Hopwood, Anderson and Creamer (2008) and Vasterling, Brailey and Sutker (2000).

If supported by further research these findings may suggest that:

- Initial sensitivity to the environment as reflected in high Olfactory Threshold scores are a predictive marker for the development of PTSD at Time 2 and amongst females at Time 3 by a factor of six.
- That in some cases the effect of PTSD is to increase the sensitisation of females to the environment. This is plausible given the trend for female participants with PTSD across the Time spans to have an increase in their Olfactory Threshold scores.

Other findings of this research were consistent with the established literature, namely that females significantly outperform males on the Olfactory Threshold task and are more likely to have PTSD. In this sample, females were 2.4 times more likely to have PTSD than males. Intuitively the results of this research make sense. As females are much more likely to incur a diagnosis of PTSD than males, and females have much greater olfactory capacity than males then, if Olfactory Threshold and PTSD were related, one would anticipate high Threshold to predict PTSD and specifically females with high Threshold strongly predicting PTSD. This is what the results indicate.

Olfactory Identification.

There was a significant interaction between Olfactory Identification and PTSD, which also changed across the year.

- Firstly, at Time 2 and 3 participants with PTSD demonstrated significant superior Olfactory Identification to those who did not have PTSD. Specifically, at Time 2 the odds of a participant with a high Olfactory Identification score having a diagnosis of PTSD was 2.7 times higher than that of a participant with a low Identification score. At Time 3 the odds of a participant with a high Olfactory Identification score having a

diagnosis of PTSD was 3.4 times higher than that of a participant with a low Identification score.

- Secondly, participants with high Olfactory Identification scores had a 3-fold increase in odds of PTSD diagnosis from Time 1 to Time 2, which remained elevated at Time 3. There was no significant change in odds of PTSD diagnosis across time for those with low Olfactory Identification scores.

These notable results suggest that the effect of PTSD in some cases is to further increase people's sensitisation to the environment. This is demonstrated by:

- Participants with PTSD at Time 2 and at Time 3 demonstrate an increase in their Olfactory Identification scores.
- Those with persisting high Olfactory Identification scores or experiencing an increase in their Identification scores at Time 2 and Time 3 are threefold more likely to develop PTSD.

Such a finding may assist in identifying those at risk of delayed onset PTSD i.e., people who go from a low to high Olfactory Identification score across time may be at higher risk of delayed onset PTSD. Further research could investigate this trend in the data.

When considering these results it is important to note the lack of a gender by Olfactory Identification by PTSD relationship. This indicated that the relationship between Olfactory Identification and PTSD over time was not different for males and females. This means that the relationship between high Olfactory Identification scores and PTSD is a robust, exclusive, stand-alone phenomenon, which is not mediated by gender. This is pertinent when considering that females are much more likely to incur a diagnosis of PTSD and have superior Olfactory Identification ability in comparison to males (Thuerauf, Reulbach, Lunkenheimer, Lunkenheimer, Spannenberger, Gossler, Maihöfner, Bleich, Kornhuber and Markovic, 2005).

Thus, possible neurohormonal factors increasing Olfactory Identification scores in those with PTSD are not gender specific but affect both genders equally. The other significant finding indicated as expected that females outperformed males on the Olfactory Identification task.

Finally, there was a trend for participants with low Olfactory Identification scores at Time 1, to be diagnosed with ASD, although this was not statistically significant. Previous research has demonstrated a robust relationship in Vietnam veterans with PTSD and low Olfactory Identification scores. Thus for this reason it was hypothesised that low Olfactory Identification scores would predate the onset of PTSD. OFC dysfunction had been considered as a possible reason for this association. Therefore, those with low scores prior to trauma were considered more neurobiologically predisposed to developing PTSD. However, the nonsignificant result in this study suggests that low Olfactory Identification scores do not predict PTSD. Thus although Olfactory Identification deficits are a significant precursor to many neurological disorders, based on these results this is unlikely with PTSD. It is possible that those with schizophrenia and associated serious mental disorder are more vulnerable to PTSD after experiencing a serious trauma, as the extremely high rate of those with PTSD in a psychiatric inpatient population testifies (McFarlane, Schrader, Bookless and Browne, 2006). However, those with active psychotic and related disorders were not included in this study.

Olfactory Discrimination.

Results demonstrated that females significantly outperform males on the Discrimination task. This result was anticipated given that a very robust finding in olfactory literature is female's olfactory superiority over males, for instance, in the task of Olfactory Identification and Threshold (Doty, Applebaum, Zusho and Settle, 1985). No relationship was found between Olfactory Discrimination and PTSD over time either as a

predictive measure or as a relationship. On reflection, this is somewhat surprising given the relationship between PTSD and Olfactory Identification and Threshold.

The initial hypothesis was that reduced Olfactory Discrimination and PTSD would be related. The reasons for this were that numerous studies have demonstrated neurocognitive impairment including explicit and working memory deficits in those with PTSD. Working memory refers to the active manipulation and short-term maintenance of information while performing complex cognitive tasks (Baddeley, 1996). For instance, an fMRI study by Shaw, Moores, Clark, McFarlane, Strother, Bryant, Brown and Taylor (2009) concluded that there was inefficient allocation of resources for differential task demands in working memory systems. Based on these and other results one would anticipate that an olfactory working memory task performed by those with PTSD would demonstrate deficits in comparison to those without PTSD. However, this premise is predicated on the same neurological regions being compromised in olfactory working memory as they are in the other senses. Researchers investigating working memory in the various sensory modalities have found that olfactory working memory does engage the same prefrontal cortical regions as the other senses. However, they did not dismiss the possibility of modality-specific neural populations within the dorsolateral or ventrolateral cortex (Dade, Zatorre, Evans and Jones-Gotman, 2001). Kareken, Mosnik, Doty, Dzemidzic and Hutchins (2003) conducted a PET scan study and found that an Olfactory Discrimination task comparing serial odours involved the hippocampus, which they concluded demonstrated olfactory working memory. Thus given that an Olfactory Discrimination task engages working memory (storage, update and comparison of odours) whether one employs a verbal representation or neural image of the odour (Yeshurun, Dudai and Sobel, 2008), one may anticipate Discrimination deficits in those with PTSD. As Olfactory Identification and Threshold was improved in those with PTSD and these tasks are an aspect of Discrimination, this may have mitigated the deficits. However, other

considerations including how soon after the trauma someone with PTSD begins to have detectable working memory dysfunction needs to be clarified. Whether significant dysfunction occurs within 3 months, as is the noticeable increase in Olfactory Identification and Threshold is unknown.

It is possible that the sequelae of chronic long term PTSD are a decrease in Olfactory Discrimination due to diminished neurogenesis, but this is for another study to determine. It is known that PTSD affects the hippocampus, a site where considerable neurogenesis takes place, with smaller size being a feature (Geuze, Vermetten and Bremner, 2005). The subventricular zone of the forebrain is also a region of prolific neurogenesis. It is here that neuronal progenitor cells migrate via the rostral migratory stream to the olfactory bulb. At the olfactory bulb, neurons ascend outwardly to the granule and periglomerular cell layers, where they differentiate into local neurons. A study examining the effects of restricted neurogenesis in the olfactory bulb of mutant mice showed impairment of Discrimination between odours but not Olfactory Threshold or short term olfactory memory.

It concluded that a critical number of newly generated neurons in the adult olfactory bulb is crucial only for odour Discrimination but not for general olfactory functions (Gheusi, Cremer, McLean, Chazal, Vincent and Lledo, 2000). Further studies have found that not only is olfactory bulb neurogenesis necessary for olfactory perceptual learning, but Olfactory Discrimination learning promotes the survival rate of newborn neurons preferentially engaged in processing of the learned odour (Moreno, Linster, Escanilla, Sacquet, Didier and Mandairon, 2009). This is a possible explanation for the Olfactory Identification deficits in those with chronic long term PTSD.

Synthesis of Findings

The possible explanation for such anomalous and unpredicted results, which indicate a relationship between Olfactory Identification, Olfactory Threshold and PTSD, will now be explored against the background of a body of more general literature. Specifically, high Threshold scores predicting PTSD and a relationship between PTSD and high Olfactory Identification scores. The following tentative conclusions can be drawn from such results.

Firstly, to summarise, to date there is no definitive explanation. The Olfactory system is exceptionally complex and much about its functioning remains unclear. For example, the well observed and predictable phenomena of Olfactory Identification deficits predating various neurological disorders have been well described but no complete explanation has yet been elucidated. There are many plausible explanations, which have been proposed, but the cause is unknown. However, given that the olfactory system has remarkable complexity it is most probable that there are a plethora of different factors and subtle processes specific to each disorder. Thus, the proposed explanation presented in this thesis is an introduction, and is to be considered in a circumspect manner.

It is hypothesised that the relationship between PTSD and olfaction may be explained by sensitisation and concomitant stress-induced neurohormonal dysregulation. The ‘increasing sensitisation model’ of PTSD as advocated by McFarlane (2010) provides an excellent framework for understanding and predicting the escalating interaction of neuropsychobiological factors over time. It includes many interacting variables such as memory, environment, neurophysiology and behaviour. The central components of the model are the dual processes of sensitisation and kindling. Collip, Myin-Germeys and Van Os (2008, p. 220) define sensitisation as the “observation that individuals who are repeatedly exposed to an environmental risk factor may develop progressively greater responses over time, finally resulting in a lasting change in response amplitude.” The

process of increasing sensitisation leads to the development of an over reactivity to a range of stimuli in the environment which finally become reminders of the traumatic event (Stein, Simmons, Feinstein and Paulus, 2007). This escalating process also provides an excellent explanation for the phenomena of delayed onset PTSD which is often preceded by sub-threshold PTSD symptoms during the first months (McFarlane, 2010).

A consequence of increased responsiveness includes greater reactivity to formerly minor contextual cues of trauma. This in turn has the effect of further sensitising the individual (Marshall and Garakani, 2002) who may then find that trauma relevant cues come to serve as unconditioned stimuli through the process of second order conditioning, thus generalising increased emotional responses to many previously neutral cues (Wessa and Flor, 2007). Thus an escalating reactivity to an emerging range of minor cues (environmental sensitisation) becomes increasingly more subtle and generalised, precipitating irrelevant reminder cues to relevant ones. Olfactory cues may also become potent triggers. This is because people are often not consciously aware of them and they are readily associated with emotion and become more evocative with trauma. This escalating progression frequently goes unrecognised, triggers unwanted intrusive memories and serves to further reinforce the distress response (McFarlane, Yehuda and Clark, 2002). This is also the possible mechanism for the development of delayed onset PTSD (McFarlane, 2010).

A much larger study (Injury Vulnerability Study) of which this study is a part, found that 2 years after trauma, approximately 25% of those diagnosed with PTSD were due to delayed-onset PTSD. Of those with delayed onset PTSD, at Time 2 (3 months), 44.1% reported no PTSD, while 55.9% had subsyndromal or full PTSD (Bryant, O'Donnell, Creamer, McFarlane and Silove, 2013). Given the relationship between PTSD and high Olfactory Threshold and Identification scores, it is possible that a feature of those with delayed onset PTSD is the change from a low to a high Identification and Threshold

score over time. This study would be worthwhile and easily conducted. The results of an earlier study of the above participants by Bryant, Creamer, O'Donnell, Silove and McFarlane (2012) found that the majority (64%) of those diagnosed with PTSD at Time 3 did not initially present with ASD. These results reflect the escalating and unpredictable trajectory of PTSD over time. However, it appears that once PTSD is established unwanted trauma memories often become increasingly more spontaneous due to the consequence of a kindling like progression (McFarlane,2010).

The process of kindling is initiated following severe trauma (and a resultant diagnosis of PTSD), with the experience of further trauma stimuli of a lesser order (perhaps trauma memories) evoking a full response. This occurs due to the increasing amplitude of the response to trauma stimuli. Conversely, the experience of similar repeated trauma stimuli evokes an even greater response, serving to further entrench PTSD (Kendler, Thornton and Gardner, 2000). As a result, this increased neuronal sensitisation eventually transitions to increasingly autonomous PTSD (McFarlane, 2010). Thus, the underlying pathophysiological system of someone with PTSD includes increased limbic volatility and arousal, which is demonstrated by increased Olfactory Identification and Threshold. For example, the results of the olfaction by PTSD relationship demonstrate that once a participant has a diagnosis of PTSD at Time 2 their Olfactory Identification score continues to improve through to Time 3. This result is also replicated in the Olfactory Threshold scores of females with PTSD whose Threshold scores increase across time. Thus, the increasing olfactory scores post PTSD diagnosis indicate a neuronal kindling process.

The process of kindling is essential to understanding the processes of the fear related neuronal circuitry, which includes the amygdala, locus coeruleus, hippocampus, and thalamus. It is based on the observation that once an illness (particularly psychiatric) has been precipitated, further episodes of the illness become more likely to occur even

when less potent triggers are involved. Eventually the illness can be precipitated almost spontaneously. The process explains how synapses will react to particular stressors and encompasses a whole range of data including the neurophysiology and neurochemistry of the onset and maintenance of chronic life-long PTSD (McFarlane, 2010). Thus with the advent of a significant trauma and a subsequent diagnosis of PTSD, the HPA axis is seized by a kindled response, which further activates marked hormonal dysregulation and global sensitisation. This response could be termed major sensitisation.

The 'increasing sensitisation model' of PTSD contends that PTSD is a unique disorder in that it is not an immutable, fixed condition, but is dynamic and involves escalating neuropsychobiological processes, which change in nature and presentation over time. Thus, an initial predictable response to trauma can amplify over time to become a disordered reaction (Yehuda and McFarlane, 1995) with the consequence that the initial activated system presents differently at later phases of PTSD. This escalation is mediated by neurohormonal and neuroanatomical dysfunctions (van der Kolk, 1997) which significantly influence the limbic system. Due to the extensive shared neurophysiology of the limbic and olfactory systems, much of the escalating neuropsychobiological process can be observed via olfactory functioning. Thus, olfaction truly becomes a window to the brain.

Olfaction then is not solely a sensor that measures and differentiates external chemical molecules. It is also a measure of internal neuropsychobiological processes, which regulate sensitivity to the external environment. This is a very important distinction. An example of this is the relationship between olfaction and satiation. In mammals, satiety is signalled by hormones which also modulate olfactory functioning. Although the relationship is yet to be unequivocally decided in humans, amongst rodents it has been well established. Fasted animals have improved olfactory sensitivity and exhibit more food-odour exploration time than do satiated ones who exhibit decreased sensitivity (Aimé,

Duchamp-Viret, Chaput, Savigner, Mahfouz and Juliard, 2007). This indicates that olfactory functioning is a mechanism by which we are able to measure internal sensory processes.

A recent publication from the Injury Vulnerability Study by Bryant, Felmingham, Silove, Creamer, O'Donnell and McFarlane (2011) established the following. Females traumatised in the mid-luteal phase (18 - 24) of the menstrual cycle are almost five times more likely to experience stronger traumatic flashback memories than females not traumatised during this period. This is also a corresponding peak period of olfactory sensitivity. In a comprehensive menstrual-cycle olfactory study, a signal detection measure was utilised to determine odour detection of females across the menstrual cycle. Olfactory sensitivity was noted to peak during the second half of menses, midcycle (ovulation), and midluteally (days 14 - 21) (Doty, Snyder, Huggins and Lowry, 1981). . Thus, a peak period of sensitivity appears to promote the amplification of trauma memories. It was hypothesised by the authors, that increased circulating levels of glucocorticoid related to the luteal phase of the menstrual cycle, may expedite these memories (Bryant, Felmingham, Silove, Creamer, O'Donnell and McFarlane, 2011). Memories especially of emotional experiences are known to be modulated by stress hormones such as glucocorticoids (Chen, Bambah-Mukku, Pollonini and Alberini, 2012). Interestingly salmon homing behaviour relies on the memorising of specific odours, which is only possible when there is a marked elevation in plasma glucocorticoid concentration during migration to natal spawning regions (Fagerlund, 1967). Perhaps it is possible that sensitisation of the HPA axis and the resultant glucocorticoid secretion play a role in increased olfactory functioning.

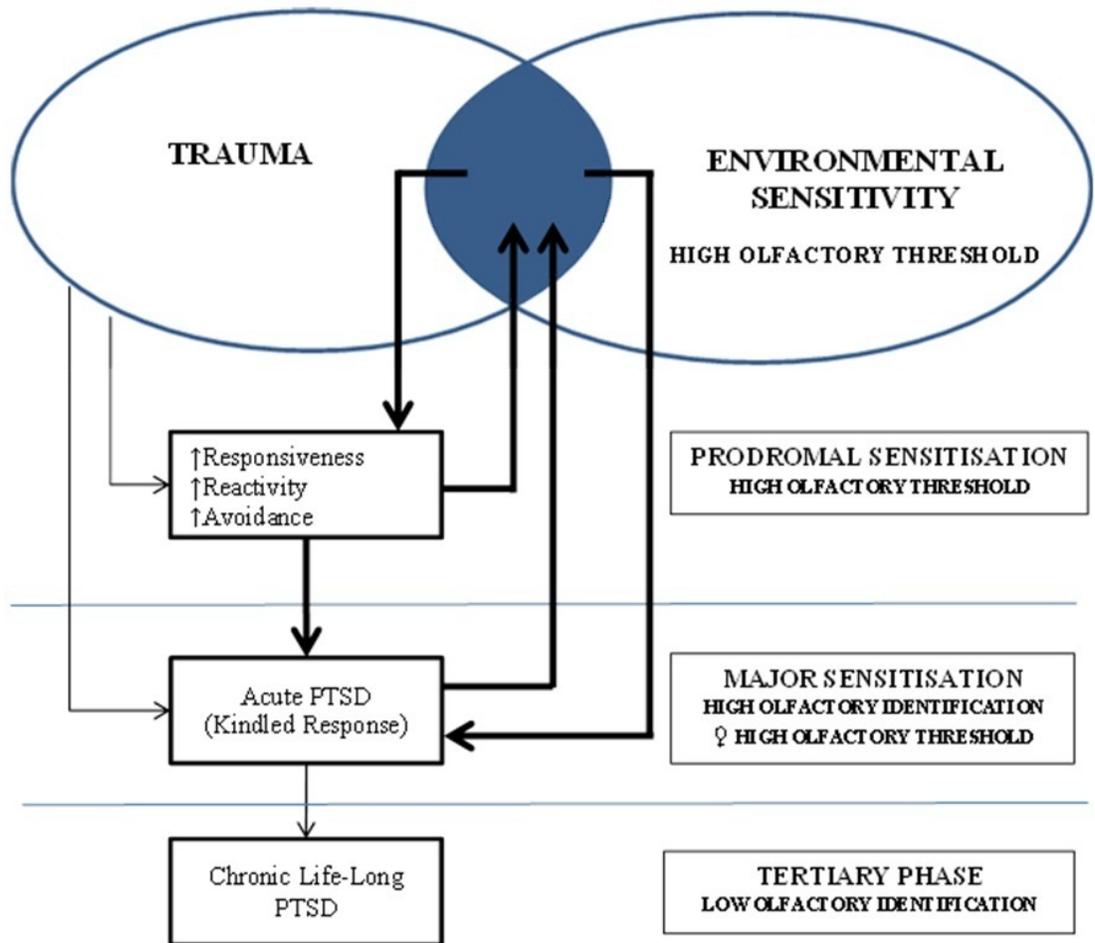


Figure 10. Model of Prodromal, Major and Tertiary Phases of PTSD.

The above proposed phases of PTSD model is able to accommodate, not only the apparent contradictory results of the study by Croy, Schellong, Joraschky and Hummel (2010) of increased Olfactory Identification and that of Vasterling, Brailey and Sutker (2000); Dileo, Brewer, Hopwood, Anderson and Creamer (2008) decreased Olfactory Identification, but also the results of this investigation.

The results of this investigation suggest a prodromal sensitisation phase which is reflected in high Olfactory Threshold scores predicting PTSD; a major sensitisation phase where Olfactory Identification and PTSD are directly related as confirmed by this study

and Croy, Schellong, Joraschky and Hummel (2010) and later a tertiary phase where long term chronic PTSD and low Olfactory Identification scores are related.

Prodromal Sensitisation

The idea of a feedback loop with different but escalating phases of sensitisation in the development of PTSD can be observed in the olfactory data of this investigation. A comparison of PTSD and its relationship to Olfactory Threshold and Identification reveals that:

- it occurs at different times.
- the nature of the relationship is different.

This suggests two phases, which share a related pathway given both fall under the rubric of olfaction but a different biological process.

Prior to a diagnosis of PTSD, there is a group of participants who exhibit significant pre-existing sensitisation to the environment. This group is defined by their high Olfactory Threshold scores, which in contrast to low Threshold scores are predictive of PTSD at Time 2 and in females at Time 3. Thus, increased sensitisation is an important vulnerability factor in the development of PTSD.

Therefore, it is hypothesised that people who are neuropsychobiologically primed and particularly sensitive to the external environment exhibit heightened Olfactory Threshold. Once exposed to trauma, people in this group could be referred to as being in a prodromal sensitisation phase.

Given that high olfactory Threshold scores at Time 1 predict PTSD at Time 2, a study that may have some merit is to investigate whether people with Olfactory Threshold score changes from low to high across the time spans are also more susceptible to PTSD. This is a possible pathway for the aetiology of delayed onset PTSD which is also a form of prodromal sensitisation.

Major Sensitisation

Considering that high Olfactory Identification does not predict PTSD across time, as does Olfactory Threshold, suggests a subtle but different process. It is proposed that once diagnosed with PTSD a kindled response occurs with a concomitant increase in Olfactory Identification. It is likely that this increased Olfactory function only serves to escalate sensitisation to the environment and exacerbate an over active HPA axis. It is suggested that this creates a feedback loop further entrenching the PTSD response as illustrated in Figure 9.

The relationship between Olfactory Identification and PTSD, is robust, not influenced by gender and appears to have three particular characteristics.

- Firstly, at Time 2 and 3, participants with high Olfactory Identification are more likely to have a diagnosis of PTSD than low Identification scorers.
- Secondly, over time the odds of those with high Olfactory Identification scores having PTSD continues to increase in comparison to those with low scores.
- Thirdly, those with high Olfactory Identification scores had a 3-fold increase in odds of PTSD diagnosis from Time 1 to Time 2, which remain elevated at Time 3. At Time 2 and 3, this cohort is composed of two groups of participants. Those with initial high scores and who remain high; those whose score became high over time. This last group i.e., participants who progress from low to high Olfactory Identification over time would be interesting to follow over the long term. It is possible that they will also present later with delayed onset PTSD.

As Olfactory Identification engages higher order brain regions such as the OFC and requires substantial cognitive functioning, it is indicative of the global nature and extent of this phase of sensitisation.

Possible explanations for increased olfactory performance include heightened OFC functioning. However although the Olfactory Identification test is a reliable measure of

OFC functioning (Li, Lopez, Osher, Howard, Parrish and Gottfried, 2010) much of its input appears to be a top down effect. For instance, the top down effect that the OFC exerts on the olfactory system when one's appetite or thirst is satiated. This occurs when individual olfactory neurons cease to fire upon satiation, thus reducing the associated sense of pleasure (O'Doherty, Rolls, Francis, Bowtell, McGlone, Kobal, Renner and Ahne, 2000). This effect is an inhibitory response not an excitatory one and is an important distinction. As a result it is unlikely that the reason for superior Olfactory Identification is due to enhanced OFC functioning.

Thus, the proposed rationale for increased Olfactory Identification is the process of increasing sensitisation resulting in the kindled reaction of PTSD and concomitant hormonal response which is subsequently reinforced by further sensitisation.

This increasing global sensitisation post PTSD could be referred to as the major sensitisation phase. Therefore, extrapolating from this data it is proposed that sensitisation in those with PTSD includes two similar but different interacting phases; the prodromal sensitisation phase and major sensitisation phase.

Tertiary Sensitisation

The Olfactory data from this and the veteran study seems to indicate that there are different phases in the aetiology, development and progression of PTSD. It is likely that these phases reflect internal neurohormonal states. The final phase is marked by significant Olfactory Identification deficits in Vietnam veterans with PTSD. These results which are contrary to those experiencing acute PTSD suggest that there are different biological substrates operational in long term chronic PTSD i.e., post 40 years which have an inhibiting effect on Olfactory Identification. It is possible that the sequelae of chronic long term PTSD are the exhaustion of neurogenesis or neurohormones, which has had a dampening effect on olfactory functioning. This phase could be termed the tertiary phase of PTSD.

Of particular note is a view that Olfactory Threshold is considered a purely biological measure with no cognitive correlates. There are several well documented reasons for this. Olfactory Threshold was defined as the lowest concentration of an odorant that was discernible. No other qualitative information was required. Thus, this evaluation allowed for a purely sensory rather than cognitive test of olfaction. This is an important distinction as it means that top down cognitive processing and an influence such as that exerted by the anterior piriform or OFC is unlikely to affect performance.

Thus, the explanation for the Threshold results is more likely to be based on sensory reasons, which are not mediated by higher cognitive processes. An fMRI study by Frasnelli, Lundström, Boyle, Djordjevic, Zatorre and Jones-Gotman (2010) endorsed this. They assessed Olfactory function and grey matter thickness and found no correlations between Threshold scores and cortical thickness. Their results also concurred with those of Jones- Gotman and Zatorre (1988) who concluded that Threshold scores are mediated by predominantly peripheral structures. Another study to determine the cognitive correlates of Olfactory functioning, such as Threshold (sensitivity), Discrimination, and Identification were also conducted. The results indicated that proficiency in executive functioning and memory contributed significantly to odour Discrimination and Identification performance, where-as cognitive factors proved unrelated to performance in the odour Threshold test (Hedner, Larsson, Arnold, Zucco and Hummel, 2010).

However, despite olfactory sensitivity not having cognitive input does not preclude it from higher order cerebral functioning. Previously olfaction was divided into two hierarchical and independent processes namely Olfactory Threshold, which was believed to involve mostly peripheral processes, and Olfactory Identification and Discrimination, which engaged more central processes. Thus, deficits in sensitivity were deemed due to epithelial dysfunction and deficits in Identification and Discrimination due to higher order cerebral functioning such as OFC dysfunction etc. (Moberg, Agrin, Gur, Gur, Turetsky and

Doty, 1999). But it appears that the reality is far more complex than initially thought. For instance, many MRI studies have demonstrated that Olfactory bulb volume is directly related to olfactory function (Rombaux, Duprez and Hummel, 2009). However, an important study by Smitka, Puschmann, Buschhueter, Gerber, Witt, Honeycutt, Abolmaali and Hummel (2012) also found that the volume of the right hippocampus showed a small but significant correlation with odour Threshold which was not mediated by age. Thus, these findings demonstrate the enormous complexity and interrelatedness of olfaction. It was concluded that the relationship between hippocampal volume and Olfactory Threshold is mediated by adult neurogenesis and synaptogenesis. One can only speculate as to whether the reason for low Olfactory Identification in veterans with PTSD is due to a reduction of neurogenesis.

One could suggest that if Olfactory Threshold is mostly regulated by biological factors as opposed to cognitive ones then these factors have a significant input into the proposed prodromal sensitisation phase. These factors are more likely to be of an inherent and long-standing nature. I.e., a trait marker such as gender, personality and heritable disposition rather than a state marker. It is not surprising then that significantly enhanced odour threshold sensitivity has been found in socially agreeable people and significantly enhanced trigeminal sensitivity in neurotic subjects. It is also possible that sensory processing which varies with personality may influence an individual's experience of the environment (Croy, Springborn, Lötsch, Johnston and Hummel, 2011). This could include increased perceptions of danger due to increased reactions (increased sensitivity) thus having implications for PTSD. Another study examining personality style and olfaction found a correlation between Olfactory Identification and traits of neuroticism, impulsivity, and unassertiveness. These traits were found to be robust predictors for successful Odour Identification, after controlling for individual variations (Larsson, Finkel and Pedersen,

2000). Interestingly McFarlane (1988) noted that introversion and neuroticism are premorbid factors significantly associated with the development of chronic PTSD.

Thus, it appears that olfactory sensitisation which occurs prior to a diagnosis of PTSD and is demonstrated by high Threshold scores is more influenced by biological factors. The characteristics of prodromal sensitisation based on the olfactory results are; it predates and predicts PTSD; is sensory in nature and is mediated by gender at 12 months post PTSD. The process of kindling and PTSD diagnosis continues this heightened olfactory awareness with an increase in Olfactory Identification scores. Consequently, PTSD increases olfactory physiology and function. It is also possible, that the heightened olfactory sensitivity demonstrated in those with PTSD has an immediate adaptive advantage. A study by Croy, Schellong, Joraschky and Hummel (2010) using chemosensory event-related potentials found that those with PTSD in comparison to those without preferentially processed unpleasant stimuli. Avoiding unnecessary danger by preventing disease encounter with olfactory cues, smelling and avoiding predators, perceiving the fear signals hidden within the body odour cocktail of others and smelling kin, are adaptive features (Lundström and Olsson, 2010) during times of threat to life.

Limitations

There were several limitations to this particular study. Firstly, the study indicates that a high Olfactory Threshold score at time of hospital admission predicts PTSD at three and twelve months. Olfaction is a stable sense and is unlikely to vary significantly in a matter of days. However to clearly demonstrate that it is a pre-existing vulnerability marker, a prospective evaluation of olfactory functioning prior and post trauma may need to be conducted.

Secondly, although initially 202 participants were recruited to the study, by Time 3 there were 146 participants, which is a retention rate of 72.7%. This is not ideal as missing data have the potential to distort the data. Despite multiple efforts to engage participants,

reasons for lack of following up included moving interstate or to the country, death, uncontactable, jail and voluntary withdrawal.

Thirdly, the duration of follow up was for 12 months only and not years. This means that a great deal of valuable olfactory data has been forgone. For instance, this study has described a robust relationship between high olfactory scores and acute onset PTSD. However as previously noted, studies of Vietnam veterans have described a relationship between low Olfactory Identification and PTSD. Barring confounding variables being the reason for low Olfactory Identification, one can only assume that chronic long term PTSD is related to low Olfactory Identification. What is not known is at what stage in chronic long term PTSD does olfactory function deteriorate? Its rate of deterioration? In addition, its concomitant psychological features?

Fourthly, at Time 1 approximately 5% of participants were receiving oxygen via nasal cannula. This is a device used to deliver supplemental oxygen to patients needing respiratory assistance. On these occasions, participants were followed up after the cannula had been medically removed or removed by themselves. It is unlikely that Olfactory Identification or Discrimination would have been greatly affected however there is likely to have been an effect on Olfactory Threshold as the oxygen may dry the epithelium.

Fifthly, approximately 15% of participants were smokers. However, at Time 1 during hospitalisation smoking was forbidden. At Time 2 and 3 although participants were asked not to smoke for 2 hours before testing, some did. Smoking has been found to be adversely associated with olfactory ability in a dose-related manner on the "Sniffin' Sticks" test (Katotomichelakis, Balatsouras, Tripsianis, Davris, Maroudias, Danielides and Simopoulos, 2007). Interestingly over time, a number of participants due to the adverse nature of their trauma experience ceased smoking.

Finally potential confounding variables such as age, previous or current mental disorder, smoking, and serious alcohol abuse were not controlled for in this study.

However the effect of these variables is to diminish olfactory functioning not increase it as was found in those with PTSD.

Further Research

Olfactory Identification has been investigated in those with chronic long term PTSD (tertiary sensitisation phase) however Olfactory Threshold and Olfactory Discrimination have not. This investigation would be very useful and add to our knowledge of the area.

Olfactory Threshold substantially increases in patients with adrenal cortical insufficiency otherwise known as Addison's disease. It is thought that hypocortisolism is the cause of the hyperosmia as it is reversed to normal by the administration of prednisolone (Henkin and Bartter, 1966). Interestingly some of the symptoms of cortisol insufficiency often appear to mimic PTSD. These include symptoms such as enhanced stress sensitivity, pain, and fatigue (Fries, Hesse, Hellhammer and Hellhammer, 2005). This is not a surprise given that low cortisol levels are often observed in those with PTSD. A cortisol by Olfactory Threshold by PTSD study is easily tested and deserves further investigation.

Given that delayed onset PTSD is a significant characteristic of this field (O'Donnell, Varker, Creamer, Fletcher, McFarlane, Silove, Bryant and Forbes, 2013) any research investigating its development is worthwhile. Therefore, given the relationship between PTSD and high Olfactory Threshold and Identification scores, it is possible that a feature of those with delayed onset PTSD is the change from a low to a high Identification and low to high Threshold score over time. Specifically is:

- a) Olfactory Threshold score changes from low to high across the time spans predictive of delayed onset PTSD.
- b) Olfactory Identification score changes from low to high across the time spans predictive of delayed onset PTSD.

Finally an investigation to determine whether high Olfactory Threshold score is a pretrauma predictor of PTSD would be a very valuable contribution to this emerging field.

Clinical Relevance of Findings

High Olfactory Threshold score is predictive of PTSD and high Olfactory Identification score increased the risk of developing PTSD. This finding is unique, however if supported by further research high olfactory sensitivity may prove to be a vulnerability marker. This suggests that olfactory testing maybe a valuable aid in the screening, prevention and treatment of those most at risk of PTSD. For example:

- As a more generic screening test prior to trauma, such as part of a selection criteria for emergency services personnel or soldiers.
- Secondly, as a post trauma-screening test for an early targeted treatment response aimed specifically at those either coursing toward PTSD or with a diagnosis of PTSD.
- Thirdly post trauma to identify, monitor and treat those who present with subsyndromal symptoms of PTSD i.e., (increasing sensitisation) which is a marker for delayed onset PTSD.

Olfaction differs from the other senses in that it bypasses the thalamus and has direct neurological links to centres for memory and emotion. For this reason odours are particularly evocative and easily conditioned. Thus, emergency service personnel with an acute sense of smell who are required to work in forensic settings maybe at greater risk for PTSD. This is especially so if the odour evokes disgust. Tests of Olfactory Threshold could determine those most sensitive who could use breathing apparatus.

Finally some members of the armed services upon discharge from active duty are bullish and have been known to ‘fake well’ during interviews with psychiatrists. This is due to the current prevailing stigma of mental illness especially amongst fit young men. However, it is difficult to manipulate the results of an olfactory test when operated by an experienced practitioner. Such a test may provide an opportunity to increase the

awareness, education and understanding of personnel who may be facing an increased likelihood of developing PTSD.

Conclusion

There is a significant and dynamic relationship between olfaction and PTSD, which reflects the escalating nature of this disorder. The driving forces behind this progression are most likely sensitisation and kindling. Specifically a primary vulnerability marker in the development of PTSD is sensitivity to the environment. This is demonstrated by initial high Olfactory Threshold scores, which predict PTSD.

Following trauma those most vulnerable can become increasingly sensitised until an episode of PTSD is precipitated. Once diagnosed with PTSD, kindled responses further sensitise people. This is exhibited by Olfactory Identification scores, which significantly increase, especially in comparison to those with low scores. The significant relationship between olfaction and PTSD means that olfactory testing has possible applications in screening and prevention.

APPENDIX A

Definition of Nontraumatic injury

All nontraumatic injury was excluded. Nontraumatic injury was defined as an injury that was minor and caused by a nontraumatic event. This included minor injury sustained by the following mechanisms of injury:

- Falling from a nonheight (e.g., tripping, slipping, fainting)
- Domestic accidents (accidents that occur around the home including in the back shed)
- Nontransportation sporting injuries (all ball and contact sports)

(However, sporting transportation accidents were included in the study. This included sporting injuries sustained by vehicles of some sort such as motor car, bike, aircraft (including gliding, parachutes), boats, boards (skiing, surfing). Thus, all injury (minor and major) that was caused by transport accidents, assaults, and height falls was included.

APPENDIX B

Definition of Mild Traumatic Brain Injury (MTBI)

A participant's MTBI status was determined from information obtained from ambulance, hospital records and ongoing assessment. A participant was identified as having a MTBI if they met the definition proposed by the American Congress of Rehabilitation Medicine (American Congress of Rehabilitation Medicine, 1993) which defines mild TBI as requiring at least one of the following: a loss of consciousness of approximately 30 minutes or less, a Glasgow Coma Scale (GCS) score of 13 - 15 after 30 minutes, and posttraumatic amnesia (PTA) not greater than 24 hours (Kay, Harrington, Adams, Anderson, Berrol, Cicerone, Dahlberg, Gerber, Goka, Harley, Hilt, Horn, Lehmkuhl and Malec, 1993).

GCS: The Glasgow Coma Scale is a method for quantifying level of consciousness (Teasdale and Jennett, 1974). It evaluates three components of wakefulness: (a) the stimulus required to induce eye opening, (b) best motor response, and (c) the best verbal response. A maximum score of 15 is obtained when a person can spontaneously open their eyes, follow simple motor commands and demonstrate orientation to time, place and person. Glasgow coma scale scores were obtained from ambulance records.

PTA: Posttraumatic amnesia (PTA) was defined as the period of disturbed memory function and disorientation following neurotrauma (Forrester, Encel and Geffen, 1994). This study utilised the Westmead PTA Scale (Marosszky, Ryan, Shores, Batchelor and Marosszky, 1998) to grade disorientation and anterograde amnesia prospectively. The scale contains two questions concerning autobiographical information; five questions to test the patient's orientation for time, date and place, three questions assessing retention of pictured objects, memory of the examiners face and name are also tested. To be classified as out of PTA a participant must be orientated for person, place and time and capable of

registering ongoing events from one day to the next. In general, the use of the Westmead to measure PTA in this study is as an exclusion criterion. That is, participants were excluded if their PTA is present for greater than 24 hours. While the Westmead PTA Scale (Marosszeky et al., 1998) was effective for identifying PTA greater than 24 hours to exclude patients, assessing PTA for MTBI inclusion criteria was more difficult. Assessment of shorter periods of amnesia was conducted retrospectively following a similar strategy to Gronwall and Wrightson (Gronwall and Wrightson, 1980). Specifically, participants will be asked to describe the event during which they received their injury, starting from just before when the injury occurred. They will then be asked “And what happened then?” until the account reaches arrival in hospital. Witnesses and ambulance records were consulted to set the times of the accident and subsequent events. For example, ambulance call time (an estimate of when the accident/injury occurred), time ambulance arrived at scene, time admitted to hospital were all noted to help identify time of amnesia. The duration of PTA will be defined as the elapsed time between the return of continuous memory and the accident. If it is greater than 24 hours, the patient will be excluded from the study.

Loss of consciousness (LOC) is routinely assessed by paramedics and emergency department medical personnel, and reported in the medical notes. The current study recorded LOC from the medical notes.

Due to the severity of injuries sustained by participants admitted to the trauma service, a decision tree was used to assist in the process of identifying MTBI.

APPENDIX C

Randomised Selection Procedure

Patients were randomly selected using an automated, numerical, stratified, random assignment procedure. Each weekday morning the automated trauma list was obtained. All those meeting exclusion criteria were removed from the list. Those meeting inclusion criteria were allocated to one of three groups; short stay (1 - 3 days), medium stay (4 - 8 days) and long stay (>8). Those in the short stay group had their name copied twice onto the list so that their name appeared three times. Those in the medium stay group had their name copied once so their name appeared twice on the list. Those in the long stay group had their name copied so that their name appear only once on the list. A random number was then generated for each name on the list using the following procedure.

In Excel,

- the surname of the patient was typed in the first column
- still in the first row but next column the allocated group number was written
- still in the first row but next column was to be the column for random numbers by writing the formula $=\text{RAND}()*(b-a)+a$

where b is the row number of the last patient and a is the row number of the first patient. The cell formula border was pulled down to select all the cells of that column. A random number appeared in each cell. The formula needed to be removed by selecting all random number cells, Edit/copy/paste special/values/OK. All patients had an assigned random number, which was placed in ascending order by selecting all columns and rows (not header row), Data/sort/no header row/column/ (random number column)/ascending/OK. Patients were ordered according to their random number in ascending order. Patients were approached according to their position on this list.

A record of this list was kept in the event that the first patient approached declined or was unavailable due to a current medical procedure.

Randomisation Decision Rules

If an individual was approached who could not be seen due to their health status (treatment or medical reasons), the next patient on the randomised list was approached. This procedure continued until a person was interviewed. All those who were approached who could not be interviewed for treatment or medical reasons were included on the randomisation list the following day, while those who were interviewed were removed from the list. Approximately one patient per day was interviewed. A patient who was randomly assigned to be assessed but was not assessed because of a non-medical reason (e.g., if visitors or other non-treatment procedures prevent the interview from occurring), were classified as 'Missed'. Patients who consented to being a part of the study during their admission but who were discharged prior to completion of the assessment had their assessment completed via telephone and self-report questionnaires returned by post. The randomisation list needed to be rerun when new patients were added to the list, which was every week day.

APPENDIX D

Glossary of Terms

- Agnosia:** An inability to interpret, classify, or contrast odours, despite being able to detect odours.
- Anosmia:** Absence of smell sensation.
- Cacosmia:** Inappropriate perception of vile or foul smelling odours, including coprosmia (smelling faeces) and necrosmia (the smell of death).
- Dysosmia:** Any distortion or impairment of the sense of smell i.e., a rotten-like smell when sniffing a rose. (However, this term is usually used to describe distortions of smell such as Cacosmia, Parosmia, Phantosmia, Heterosmia and Agnosia).
- Heterosmia:** An inability to distinguish between certain odours.
- Hyperosmia:** An overly acute sense of smell.
- Hyposmia:** A diminished sense of smell.
- Normosmia:** A normal sense of smell.
- Parosmia:** A distorted sense of smell in that there is a sensation of smell in the absence of appropriate stimulus.
- Phantosmia:** Olfactory hallucinations. I.e., The presence of a smell when no stimulus is present).

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