

**Volume 1: Recall of ‘trauma-related’ events following nitrous oxide: linguistic
and psychophysiological correlates of recall.**

Susannah Hughes

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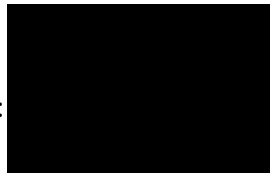
University College London

UCL Doctorate in Clinical Psychology

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Name: Susannah Hughes

Date: 30/10/2019

Overview

This thesis aimed to advance the field of knowledge into declarative recall of trauma memory. Investigations into trauma narratives have consistently confirmed that PTSD is associated with deficits in verbal memory, as well as over general autobiographical memory, avoidance or suppression of memories, and negative interpretation of memory symptoms. Chapter one investigated through a systematic search of the literature whether specific linguistic markers, such as greater use of negative affect words, insight and causation words could be identified within trauma narratives in an adult population. The review concluded that analysing trauma narratives enables us to understand the memory disturbances linked to post traumatic stress disorder and thus to develop increasingly effective psychological interventions to promote trauma adaptation. The linguistic correlates of trauma identified in chapter one were used to inform which linguistic markers should be analysed in chapter two, “recall of ‘trauma-related’ events following nitrous oxide: linguistic and psychophysiological correlates of recall”. Together with linguistic correlates of trauma, chapter two investigated the relationship between nitrous oxide inhalation and physiological changes (heart rate variability) during encoding and recall. Early pharmacological interventions have been found to hold some promise in reducing the emergence of PTSD symptoms, possibly by preventing or reducing initial consolidation of traumatic memories. Clinical findings support the utility of novel pharmacological tools targeting NMDA receptor subunits and NMDA receptors have been shown to play an important role in memory reconsolidation. Using existing data, the current study sought to extend a recently published study on nitrous oxide and involuntary emotional memories using the ‘trauma video’ paradigm. The final chapter provided a critical appraisal of the

work undertaken in the current thesis. This included critical reflection on the process of undertaking research into declarative recall of trauma memory.

Impact Statement

This thesis provides a novel investigation into declarative recall of trauma memory. To the best of our knowledge, chapter one is the first systematic review investigating linguistic markers of trauma narratives. Similarly, chapter two is the first empirical study describing the effects of nitrous oxide on declarative and psychophysiological aspects of emotional memory. The outcomes of which may have implications for the treatment and prevention of post-traumatic stress disorder.

Despite impairment in involuntary emotional memory, the results of this study concluded that nitrous oxide does not appear to degrade declarative memory. Since the latter is required for contextualisation of trauma memories, this finding suggests that nitrous oxide's beneficial effects on trauma memory are not counteracted by impairment in 'verbally accessible' memory of the traumatic memory (the main technique of exposure-based psychotherapy for post-traumatic stress disorder). Accordingly, further research is needed to continue investigating ways of detecting emotional arousal (e.g. fear and perceived threat) and different states of consciousness such as depersonalisation, derealisation, and flashbacks during voluntary recall of trauma among individuals with post-traumatic stress disorder.

Further research into the use of nitrous oxide is required to replicate these effects in a clinical sample and establish the potential benefits and dangers of its use following traumatic events. As nitrous oxide is an effective and portable analgesic, it is already very widely used by emergency services for pre-hospital pain management. The outcome of such investigation could have substantial real world effects. For example,

it is possible that this practise has unintended (beneficial or deleterious) effects on maladaptive memory formation in the post trauma period. Prospective studies of the development of maladaptive memory following traumatic events where nitrous oxide (or indeed other NMDAergic analgesics, such as ketamine) has been administered as a first-line analgesic will be useful in determining the extent of such effects.

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Part 1. Literature Review

Linguistic markers of trauma narratives: A systematic review of the literature

Abstract

Aims: To investigate whether specific linguistic markers (using the linguistic inquiry and word count programme) can be identified within trauma narratives in an adult population.

Method: PsychINFO, Web of Science and MEDLINE were searched using terms related to linguistic processes (including linguistic inquiry and word count, language, narrative coherence, cognitive process, content analysis, discourse analysis, language) and post-traumatic stress disorder. The search yielded 1839 papers, 42 of which were retrieved in full. Of these, 16 met criteria for the final analysis on the basis of our inclusion criteria.

Results: We found support for linguistic correlates of trauma, which were not observed following exposure to a less traumatic incident or control event. Specifically, markers included biological processes (sensory/body words), affective processes (positive emotion words, negative emotion words), cognitive processes (words indicative of psychological distancing, intimacy words, causation/cognitive mechanisms language, insight words), linguistic processes (faults in using present tense, first person personal pronoun, number of sentences), personal concern processes (death words), relativity processes (motion descriptors, e.g. 'arrive' or 'go').

Conclusion: This review found evidence for specific linguistic features associated with trauma narratives. Analysing trauma narratives enables us to understand the memory disturbances linked to PTSD and thus to develop increasingly effective psychological interventions to promote trauma adaptation.

1.0 Introduction

1.1 Post-traumatic stress disorder risk factors

Post-Traumatic Stress Disorder (PTSD) is a severe mental disorder with a profound public health impact due to its high prevalence, persistence, and associated functional impairment (Kessler, 2000; Ben-Zion et al. 2018). PTSD symptoms are commonly observed shortly after trauma exposure and their initial severity has been associated with higher risk of non-recovery (Galatzer-Levy et al. 2014; Stein et al. 2016).

Originally, PTSD was conceptualized as a normal response to overwhelming psychic trauma (Brewin et al., 2000). Partly on the basis of accumulating evidence for wide variation in the prevalence of PTSD following exposure to different kinds of stressors, there is increasing acceptance that exposure to a trauma is not sufficient to explain the development of PTSD (Brewin et al., 2000) and that (pre-trauma) individual vulnerability factors have a role to play in understanding this condition (e.g., Yehuda, 1999; Yehuda & McFarlane, 1995). The impact of trauma intensity, pretrauma risk factors, and other aspects of vulnerability has been reviewed by, among others, Shalev (1996) and Brewin et al., (2000).

Brewin et al. (2000) conducted meta-analyses on 14 separate risk factors for PTSD, including the moderating effects of various sample and study characteristics, e.g. civilian/military status. Three categories of risk factor emerged: Factors such as gender, age at trauma, and race that predicted PTSD in some populations but not in others; factors such as education, previous trauma, and general childhood adversity

that predicted PTSD more consistently but to a varying extent according to the populations studied and the methods used; and factors such as psychiatric history, reported childhood abuse, and family psychiatric history that had more uniform predictive effects. The authors report that individually, the effect size of all the risk factors was modest, but factors operating during or after the trauma, such as trauma severity, lack of social support, and additional life stress, had somewhat stronger effects than pre-trauma factors.

In their paper presenting two longitudinal studies exploring neurocognitive domains in recent trauma survivors, Ben-Zion et al., (2018) highlight that studies of stress exposure present significant heterogeneity in symptoms trajectories. This suggests a heterogeneity of underlying neurobiological mechanisms (Galatzer-Levy et al., 2013; Ursano et al., 1999; Shalev et al., 2012). Neurocognitive deficits linked with the emergence of PTSD (Shalev et al., 2017; Scott et al., 2015) concern working memory, speed and verbal learning, information processing, and short-term and declarative memory (Johnsen & Asbjørnsen, 2008; Samuelson, 2001), attention, and executive functioning (Aupperle, et al., 2012; Polak et al., 2012).

PTSD has been repeatedly associated with difficulties in response inhibition, attentional switching and flexibility (Casada & Roache, 2005; Hart et al., 2017; Koenen et al., 2001; Leskin & White, 2007), and these features have been linked with difficulties disengaging attention from salient stimuli (Pineles et al., 2009). Neuroimaging studies of PTSD patients have similarly documented altered prefrontal network activity in tasks requiring inhibition and attentional switching (e.g., Bryant et al. 2005 & Falconer et al., 2008). These neurocognitive targets may serve as risk-

resilience factors for the development and/or maintenance of post traumatic symptoms (Ben-Zion et al., 2018). Evidence has also shown better neurocognitive function to be associated with lower rates of PTSD diagnosis (Kaplan et al., 2002). Ben-Zion et al. (2018) concluded from their longitudinal investigations that cognitive flexibility assessed shortly after trauma exposure, emerged as a significant predictor of subsequent PTSD symptom severity. The authors suggest that these findings support further research into the implementation of mechanism-driven neurocognitive preventive interventions for PTSD.

1.2 Linguistic features of trauma

Evidence suggests that there is significant heterogeneity in psychological responding following exposure to traumatic events (Kleim et al., 2018, Bonanno et al., 2011). Many individuals demonstrate a high degree of resilience and are able to continue functioning without significant emotional and cognitive disruption whilst others develop high levels of distress and impairment associated with psychological disorders, including post-traumatic stress disorder (PTSD) (Kleim et al., 2018). Identifying predictors of adjustment trajectories is therefore necessary to help mitigate the long-term emotional, social, and health impacts following traumatic events (Visser et al., 2017).

Evidence has demonstrated that the way in which traumatic experiences are recalled and 'self-narrated' is related to symptom expression (Crespo & Fernandez-Lansac, 2016; O'Kearney & Perrott, 2006). Findings have emphasized four areas of narrative

content related to symptoms: emotion references, sensory details, cognitive processes, and temporal focus (Booker et al., 2018).

1.2.1 Narrative coherence

In his 2018 review into memory and phenomenology, Brewin notes that studies have consistently recognised that the trauma narratives of patients with PTSD are more disorganised and fragmented than both their own non-trauma narratives and the trauma narratives of individuals without PTSD (Brewin, 2018).

Investigations into trauma narratives have consistently confirmed that PTSD is associated with deficits in verbal memory, as well as over general autobiographical memory, avoidance or suppression of memories, and negative interpretation of memory symptoms (Brewin, 2018). These are likely to play a causal role in the development or maintenance of PTSD (Brewin, 2011). In addition, memories for the traumatic event itself are typically seen as altered in two distinct ways: There is impairment in the *voluntary* retrieval coupled with increased *involuntary* memory, experienced as a dissociative alteration to the sense of time (sometimes referred to as a “flashback”; Ehlers et al., 2004; Hackmann et al., 2004). What appears to distinguish intrusive memories in PTSD is that they are experienced as though they are happening in the here and now (Bryant et al., 2011; Schönfeld & Ehlers, 2017; Brewin et al., 2009; Kleim et al., 2013). The Diagnostic and Statistical Manual of mental disorders 5th edition (DSM-5; American Psychiatric Association, 2013) now clarifies that this symptom exists on a continuum from a brief sense of the event happening again in the present to a total absorption in the traumatic memory with loss of awareness of the

current environment (Brewin, 2018). The conceptualization of PTSD in the International Classification of Diseases 11th Revision (ICD-11; World Health Organisation, 2018) has identified this specific form of re-experiencing (whether as part of flashbacks, intrusive memories, or nightmares) as required for the diagnosis.

1.2.2 Cognitive and emotional linguistic features

Cognitive impairment in trauma narratives are often characterised as both a fragmentation and disorganization in the trauma memory record (Foa et al., 1995). Fragmentation, or a lack of flow in the narrative, is operationalised as consisting of repetitions, unfinished thoughts and speech fillers (Brewin, 2016). Disorganisation is operationalised as utterances which imply confusion or disjointed thinking in contrast to utterances indicating decision making, or planning which are coded as organised thoughts (Foa et al., 1995; Brewin, 2016).

However, the idea of narrative fragmentation (reflecting fragmentation in memory) has been disputed by some autobiographical memory researchers such as Rubin et al., (2016) and Bernsten et al., (2003) who propose that, “Instead of leading to disintegration, highly emotional and (thus) distinctive events may help to keep the autobiography integrated by forming reference points for the organization of other less distinctive events” (Bernsten et al., 2003, p. 678). Consistent with this notion, Porter and Birt (2001) compared the narratives of 306 undergraduates of their most traumatic and most positive events and found no difference in coherence of these narratives.

When challenging this conclusion, Brewin (2016) argues that many of Rubin and Bernstein's early investigations of memory fragmentation (Berntsen et al., 2003; Rubin, Dennis, & Beckham, 2011; Rubin, Feldman, & Beckham, 2004) relied on single-item self-report measures applied to the memory as a whole (e.g., "When you recall the traumatic event, do you then think of it as a continuous series of episodes or as some isolated incoherent fragments?"). In one study (Rubin et al. 2011) memory judgements were aggregating across a number of important, positive and stressful events, rather than focusing on exclusively on traumatic events; the authors found no differences between PTSD patients and control participants on a measure of narrative coherence (assessed using the item: "It [the event] comes to me in words or in pictures as a coherent story").

In his 2016 review into trauma memory coherence, Brewin concludes that when producing a well-rehearsed, global narrative whereby the individual focuses on the outline of the trauma story, trauma and non-trauma memories are essentially similar in their levels of coherence (Brewin, 2016). However, when focusing in on the highly detailed, most frightening components of the trauma narrative ("hotspots") disorganised and fragmented thoughts will be present. Brewin notes that some of these effects may be produced by spontaneous reliving interrupting the expression of the trauma memory (Brewin, 2007).

Brewin's (2016) revised formulation of trauma memory impairment incorporates separate evidence that exists for fragmentation in memory associated with intensely emotional moments, including the experience of flashbacks (Brewin, 2015), dissociation (Harvey & Bryant, 1999), hot spots (Holmes et al., 2005), memory gaps

(Ehlers et al., 2004), and spontaneous verb tense shifts (Hellowell & Brewin, 2004; Pillemer, Desrochers, & Ebanks, 1998). Studies specifically investigating memories for the worst moments of a trauma found that in individuals with PTSD, these moments involved more unfinished thoughts, fewer words indicating reflective processing, and more words in the present tense than the remainder of the narrative, which was not the case for the non-PTSD comparison sample (Jelinek et al., 2010). Studies have also indicated that trauma narratives also include multiple cognitive processing utterances (i.e., words like “understand,” “cause”) (Booker et al., 2018).

Recollections of traumas tend to be accompanied by negative emotions and sensory and/or perceptual information (Booker et al., 2018). For example, emotional and sensory utterances have been shown to coincide with poorer outcomes, including more severe depression and posttraumatic symptoms (Eid et al., 2005; Hellowell & Brewin, 2004). Existing literature is mixed about the relationship between PTSD symptoms and the occurrence of affect-laden words of different valence (neutral, positive, negative) (Marshall, 2016). For example, Crespo et al.’s 2016 meta-analysis conducted on 22 studies of trauma narratives found that use of negative emotion words, but not general affect was related to increased PTSD symptoms. An affect-laden narrative is consistent with the cognitive model of PTSD (Ehlers & Clark, 2000), such that individuals who have not processed their trauma are more likely to use affect words, typically negative emotion words (Eid et al., 2005; Crespo et al., 2016). However, other studies, including a meta-analysis conducted by O’Kearney & Perrott (2006) found that affect words in general (including positive as well as negative words) were prominent within narratives produced by individuals suffering from PTSD. Similarly, Jaeger et al., (2014) reported that in female assault survivors, an

increased use of both positive and negative emotion words was related to PTSD symptom severity.

A number of studies have found that trauma narratives tend to overemphasize the present tense (Hellowell & Brewin, 2004; Jelinek et al., 2009), with references to the present coinciding with greater psychological symptoms (Romisch et al., 2014). Similarly, narratives that emphasise the past tense have been found to coincide with fewer psychological symptoms (Manne, 2002). These findings correspond with temporal self-appraisal theory and views of subjective distancing (Booker et al., 2018), wherein individuals are motivated to evaluate negative past events as more distant, regardless of objective time, and benefit from distancing the self from painful experiences (Peetz & Wilson, 2008; Wilson & Ross, 2003).

1.3 Linguistic Inquiry and Word Count (LIWC)

Narrative aspects of PTSD are typically elicited using semi-structured questionnaires with open-ended questions assessing PTSD symptoms and/or individual beliefs about trauma memory. Latent Semantic Analysis (LSA) has been used to assess organization (recording semantic similarities between two texts) and the Linguistic Inquiry and Word Count (LIWC) computer programme has been used to measure various emotional, cognitive, and structural text components.

Linguistic elements of text refer to both form and content (Pennebaker, Francis, & Boothe, 2001). Form includes verb tense, prepositions, pronouns and structure of text. Content includes descriptive elements such as words related to emotion, sensation,

thought, and action, as well as nouns, and verbs. In general, the frequency of first-person singular pronouns tend to correlate positively with psychological distress (Rude, Gortner, & Pennebaker, 2004; Wolf et al., 2007) and verb tense may communicate individuals' focus on an event, e.g. use of present tense when describing past events may indicate unresolved feelings about the event (Tausczik & Pennebaker, 2010). Similarly, use of words reflective of cognitive mechanisms (e.g. "think", "believe") tend to reflect attempts to reappraise or 'make meaning' of events (Andrea et al., 2001). Other studies have suggested that the use of causal words increases during recollection of upsetting events (Boals & Klein, 2005), which correlates with *alleviation* of distress, perhaps because individuals are attempting to understand and resolve the event (Kross & Ayduk, 2008).

The Linguistic Inquiry and Word Count (LIWC) (Pennebaker et al., 2007) programme was developed to provide an effective and efficient (automated) method for studying the various emotional, cognitive, and structural components of verbal and written speech. It has been designed to serially analyse written (transcribed) text in electronically stored ('txt') files. As each target word is processed, a dictionary file is searched for matches (Pennebaker et al., 2007). LIWC analyses text and specifies general descriptor categories (total word count, words per sentence, percentage of words captured by the dictionary, and percent of words longer than six letters), standard linguistic dimensions (e.g., percentage of words in the text that are pronouns, articles, auxiliary verbs, etc.), word categories tapping psychological constructs (e.g., affect, cognition, biological processes), personal concern categories (e.g., work, home, leisure activities), paralinguistic dimensions (assents, fillers, non-fluencies), and punctuation categories (periods, commas, etc).

LIWC has been used widely within the PTSD literature (e.g. van Minnen et al., 2002 & Jaeger et al. 2014) when examining trauma narratives. For example, Jaeger et al. (2014) found that the content of trauma narratives rather than the structural aspects of the narrative (i.e. the specific words descriptors used rather than the relationship between them) may be more strongly associated with trauma related reactions. This finding is in keeping with PTSD treatment trials which have failed to find changes of trauma narrative fragmentation associated with recovery rates (van Minnen et al., 2002).

1.4 Current study

The current study aimed to systematically review empirical papers published in three electronic databases that have analysed trauma narratives using linguistic procedures, specifically LIWC. It aimed to answer the following questions:

- (1) What linguistic markers are present in trauma narratives?
- (2) How can these markers be categorised?

Results were organised according to the main narrative characteristics studied to date: (a) affective processes (e.g. positive and negative emotion words) (b) cognitive processes (e.g. intimacy, causation and insight words) and (c) linguistic processes (including tense and use of pronoun).

2.0 Method

2.1 Data sources

A systematic literature search was carried out using three electronic databases (PsycINFO, Web of Science and MEDLINE) on 19/09/2018. Search terms related to linguistic processes were combined with terms associated with post-traumatic stress disorder. In order to ensure search terms were comprehensively examined in each database, terms were searched using both specific phrase searching, e.g. “LIWC” as well as subject heading and key word searches, e.g. discourse analysis.

Search terms relating to linguistic processes were intentionally inclusive. This was because the field investigating use of language in trauma samples is relatively narrow and there were risks of studies being missed if limited to an exclusively language-only based search. For example, instead of explicitly using the term “language” in the titles, two studies (Graves et al., 2005 & Guastella & Dadds, 2006) included in the review used “emotional expression” and “cognitive and emotional organisation” and neither used language as key terms. Specifically, search terms for these studies included, “emotional expression, emotional recognition, controlled comparison, cancer” and “emotion-processing, cognitive-behavioral, writing, disclosure, trauma”.

2.2 Inclusion criteria

42 studies were retrieved in full following exclusion of 1718 studies not thought to have direct relevance to the current review. Studies were assessed using the following inclusion criteria:

(1) The sample included only adults (18+). (2) They had been exposed to a traumatic incident or received a diagnosis of PTSD (following either SCID interview or the authors stated this without elaborating on how the diagnosis was obtained). (3) Linguistic processes (emotional and/or cognitive) were examined and recorded as outcomes. (4) Studies used LIWC to analyse data. (6) Studies were published in a peer-reviewed journal. (7) Studies were reported in English.

There was no restriction on inclusion based on severity of trauma. Some studies included participants with a verified diagnosis of PTSD, and others included exposure to a traumatic incident. In studies using comparison groups, these consisted of either psychiatric controls, no PTSD diagnosis or exposure to a less traumatic incident relative to the experimental group (see figure 1). Although the review included a range of traumatic experiences, for the purpose of the current review trauma has been defined as “events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others” (American Psychiatric Association, 1994, p. 427).

Studies meeting these criteria were subjected to quality and relevance assessment (see appendix 1-3).

<p>Population: Adults (18+)</p> <p>Exposure: Traumatic event (defined as “events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others” American Psychiatric Association, 1994, p. 427).</p> <p>Comparator: Where there was a comparator, this was either no PTSD or a exposure to a less traumatic incident.</p> <p>Outcome: Linguistic markers of PTSD within a trauma narrative using the LIWC programme.</p>
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Figure 1. Summary of review inclusion criteria.

2.3 Study quality

Study quality was assessed using the National Institute for Health and Care Excellence (NICE; 2012) methodology checklists. Dependent on the study design, studies were assessed using either the randomised controlled trials methodology checklist (appendix 1), cohort studies methodology checklist (appendix 2) or case control studies methodology checklist (appendix 3).

The NICE checklists consist of between 20-25 items assessing the quality of studies' methodology and findings. They include a combination of qualitative and quantitative items. On the basis of the measure, studies were provided with a rating of “high”, “medium” or “low”.

Search Terms	Databases	Number of Articles
“LIWC”OR “Linguistic inquiry and word count” OR “narrative coherence” OR Language OR Cognitive processes OR Words (phonetic units) OR Discourse analysis OR Content analysis OR Linguistics AND Posttrauma* OR PTSD OR Post Traumatic Stress Disorder	PsycINFO	n = 1209
	Medline	n = 259
	Web of Science	n = 519
Total number of articles (without duplicates)		N = 1839

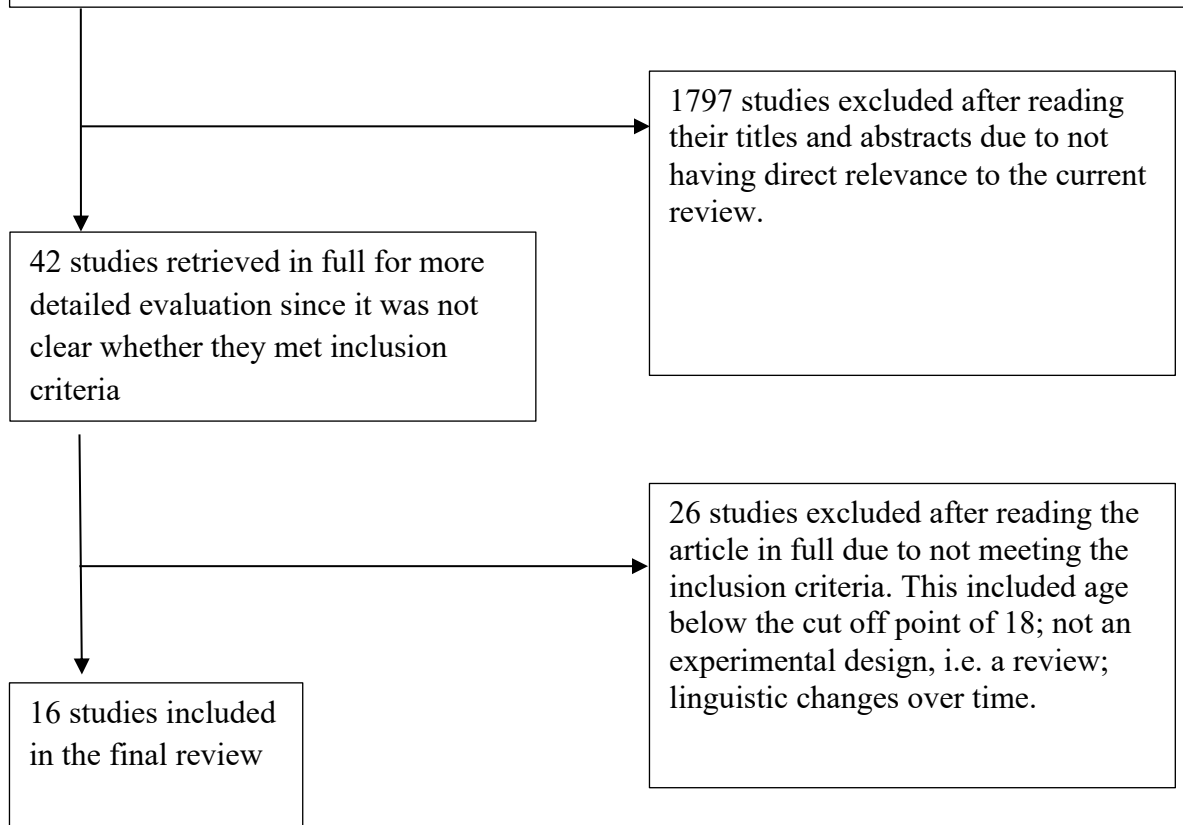


Figure 2. Literature search strategy

3.0 Results

The general aim of studies included in the review was to examine the prevalence of certain linguistic features arising as a result of exposure to a traumatic event relative to a control. In studies not using an experimental design, the focus was in relation to trauma severity (e.g. example, comparing linguistic features of traumatic vs non-traumatic memories).

The systematic search identified 1839 studies (excluding duplicates). Of these, 1781 studies were screened and excluded on the basis of relevance following review of the abstracts. The remaining 42 studies were retrieved in full for more detailed evaluation. 35 studies were excluded due to not meeting the review inclusion criteria. 16 studies were included in the current review and subjected formal quality and relevance assessment (see Figure 2). These studies are summarised in Table 1.

Table 1. Summary of studies included in review

Study	N	Gender	Age range	Exposure Group (n)	Comparison Group (n)	Study Design	Study Quality Rating
Lorenz & Meston (2012)	227	F	M = 32.7 SD = 11.5	Childhood sexual abuse (n = 128)	No childhood sexual abuse (n = 99)	Case control	Good
Jelinek, Stockbauer, Randjbar, et al. (2010)	80	M & F	M = 40 SD = 12	Trauma + PTSD (n = 25)	Trauma + no PTSD (n = 55)	Case control	Good
Guastella & Dadds (2006)	199	M & F	M = 24.2 SD = 7.75 Range = 16-56	Emotional memory/trauma writing task (n = 118)	Non emotional memory writing task (n = 81)	RCT	Good
Hoyt & Yeater (2011)	120	M & F	M = 21.2 SD = 5.5 Range = 18-57	Expressive writing - PTSD symptoms (n = 60)	Non emotional memory writing task (n = 60)	Case control	Good
Wardecker, Edelstein, Quas, et al. (2017)	55	M & F	M = 23.60 SD = 3.79 Range = 18-30	Childhood sexual abuse	No control	Correlational	Good
Graves, Schmidt, Bollmer, et al. 2004	50	F	M = 57.8 SD = 10.5	Breast cancer patients (n = 25)	Non-breast cancer control (n = 25)	Case control	Medium
Manne (2002)	82	M & F	M = 40 Range = 22-58	Parents of Pediatric Cancer Survivors	No control	Correlational	Good
Andrea, Chiu, Casas & Deldin (2012)	40	M & F	Range = 18-20	Trauma narratives following 9/11	No control	Longitudinal	Medium
Alvarez-Conrad, Zoellner & Foa (2001)	28	F	M = 31.1 SD = 9.9	Sexual assault survivors with a PTSD diagnosis	No control	Repeated measures	Medium
Ng, Ahishakiye, Miller & Meyerowitz (2015)	61	M & F	Not stated (inclusion criteria = 18+)	Genocide survivors	No control	Longitudinal	Medium
Booker, Graci, Hudak, et al. (2018)	68	M & F	Range = 19-61	Exposure to traumatic event	No control	Longitudinal	Good

Waters, Bohanek, Marin & Fivush (2013)	108	M & F	M = 19.4 SD = 1.5 Range = 18-27	Recall of intensely negative life event	Recall of neutral event	Repeated measures	Medium
Papini, Yoon, Rubin, et al. (2015)	53	M & F	M = 36 SD = 12 Range = 18-65	Trauma + PTSD (n = 23)	Trauma + no PTSD (n = 30)	Case control	Good
Owen, Giese-Davis, Cordova et al. (2006)	71	M & F	M = 56.3 SD = 10.7 Range = 30-80	Cancer survivors	No control	Correlational	Medium
Rubin (2011)	30	M & F	Range = 18-22	Trauma + PTSD (n = 15)	Trauma + no PTSD (n = 15)	Case control	Medium
Eid, Johnsen & Saus (2005)	120	M	Range = 18-29	Trauma exposure in a military sample – high emotion writing task	Neutral writing task	Repeated measures	Good

3.1 Study quality

All studies included in the review were rated as either “medium” or “good”. This ensured that data was categorised consistently across studies. All studies used a trauma experimental group and all used linguistic markers as an outcome. The primary methodological limitation across studies was small sample sizes. Demographic comparison across studies revealed predominantly female samples, which is in line with epidemiological evidence showing a greater prevalence of PTSD in women.

When examining the quality of studies on an individual basis, most demonstrated good internal validity (e.g. addressing an appropriate and clearly focused question; applying the same exclusion criteria for cases and controls, such as age below 18, mental health screen for potentially confounding disorders; exposure status measured in a standard, valid and reliable way).

However, determining the generalisability of results across studies (including drawing comparisons between studies) was more challenging. For example, although the focus of outcomes included in the review was on linguistic processes within trauma narratives, the context relative to study aims varied (please see tables 2 and 3). For example, Lorenz and Meston (2012) looked at sexual functioning and satisfaction as an outcome and the Graves et al. (2004) and Owen et al. (2006) looked at emotional expression as predictors of adjustment to cancer.

Although the inclusion criteria for the review included exposure to a range of traumatic events (see page 14), within experimental groups, this did vary substantially. This included participants exposed to genocide, sexual abuse in a PTSD sample, cancer survivors, and recalling an intensely negative life event (please see tables 2 and 3). However, participants' rating of trauma (including self-report measures such as The Trauma Symptom Checklist, The Posttraumatic Diagnostic Scale, The PTSD Symptom Scale) was generally well reported across samples. Therefore, whilst the traumatic event differed across studies, the subjective ratings of distress was consistently well reported by authors.

There were also variations with regard to the timings of when trauma occurred. This ranged from immediate aftermath (data collected in an A&E department) to childhood sexual abuse occurring years/decades previously. Booker et al. (2008) recognise that few studies have examined narratives shortly after the trauma, before memory is consolidated. The authors found that how individuals immediately began to create meaning from a traumatic experience predicted symptom trajectories. They found that,

regardless of time, individuals who used more cognitive processing utterances in the context of fewer past-focused utterances were at risk for sustained symptoms across a 12-month period. This finding was consistent across studies included in this review (e.g. Jelineck et al. 2010; Hoyt & Yeater, 2011; Andrea et al. 2012). Similarly, although variations with regard to the timings of when the trauma occurred, the impact of distress and level of current trauma at the time data were collected and well reported across studies.

Table 2. Linguistic markers examined in the 'exposed'/PTSD groups

Linguistic Marker												
Study	Number of sentences	Positive emotion words	Negative emotion words	Intimacy words	Sensory/ body words	Proprioceptive information/ motion descriptors	Words indicative of psychological distancing	Faults in using present tense	First person personal pronoun ("I" usage)	Causation/ cognitive mechanisms language	Insight	Death-related words
Lorenz & Meston (2012)		**	*	*	**		*		*			
Jelinek, Stockbauer, Randjbar, et al. (2010)			*					*		*		
Guastella & Dadds (2006)			*		*	*		*				
Hoyt & Yeater (2011)	**	**								**		
Wardecker, Edelstein, Quas, et al. (2017)				**								
Graves, Schmidt, Bollmer, et al. 2004		**	**									
Manne (2002)		*						**				

Andrea, Chiu, Casas & Deldin (2012)			**						*	*		
Alvarez-Comrad, Zoellner & Foa (2001)		*	*									
Ng, Ahishakiye, Miller & Meyerowitz (2015)	*		*	**							**	**
Booker, Graci, Hudak, et al. (2018)								*	*	*		
Waters, Bohanek, Marin & Fivush (2013)		*	*					*	*	*		
Papini, Yoon, Rubin, et al. (2015)			*						*	*	**	**
Owen, Giese-Davis, Cordova et al. (2006)		**	**							*	*	
Rubin (2011)		*	*	**					*	*		
Eid, Johnsen & Saus (2005)		*	**									

* p < .005 ** p < .001

Table 3. LIWC output variable summary

Overarching process variables	Category markers	Number of studies that found significant associations within trauma narratives (%)	Number of studies that did not find significant associations within trauma narratives (%)
Psychological processes			
Biological	Sensory/body words	4 (25%)	0
Affective	Positive emotion words	10 (62.5%)	1 (6.3%)
	Negative emotion words	14 (87.5%)	1 (6.3%)
Cognitive	Words indicative of psychological distancing	1 (6.3%)	0
	Intimacy words	1 (6.3%)	0
	Causation/cognitive mechanisms language (e.g. realize, understand, should)	5 (31.3%)	3 (18.8%)
	Insight	2 (12.5%)	3 (18.8%)
Linguistic Processes	Faults in using present tense/use of past tense	5 (31.3%)	0
	First person personal pronoun	4 (25%)	0
	Number of sentences	1 (6.3%)	0
Personal concern processes	Death words	2 (12.5%)	0
Relativity	Proprioceptive information/motion descriptors (e.g. 'arrive' or 'go')	1 (6.3%)	0

3.2 Linguistic markers of trauma

LIWC outcome variables can be divided into the following categories (as determined by Pennebaker et al. (2007):

(1) Psychological processes including biological, affective and cognitive dimensions. Biological dimensions include sensory/body words. Affective dimensions include positive emotion words and negative emotion words. Cognitive dimensions include words indicative of emotional distancing, intimacy words, causation/cognitive mechanisms language (e.g. realize, understand, should, because, effect) and insight (e.g. think, know, consider).

(2) Linguistic processes include: number of sentences, faults in using present tense, first person personal pronoun.

(3) Personal concern processes includes: death related words.

(4) Relativity processes includes: Proprioceptive information/motion descriptors (e.g. 'arrive' or 'go').

Across studies the number and type of linguistic markers examined varied (see table 3). For example, only one of sixteen studies examined “words indicative of psychological distancing” whereas 13/16 studies examined “negative emotion words”. The linguistic marker examined varied according to the wider focus of the study (e.g. use of “death related words” within a genocide survivor sample; Ng et al., 2015)

alongside previously documented evidence supporting investigation (e.g. “negative emotion” words in a study into the effects of negative emotion and expressive writing on PTSD symptoms; Hoyt & Yeater, 2011).

Most studies focused on examining psychological processes (cognitive and emotional factors) in relation to trauma narratives. All except one study, a longitudinal follow up of trauma narratives of healthy participants exposed to a traumatic incident (Booker et al., 2018) found support for greater use of affective language relative to their controls.

Sampling varied with regard to clinical and non-clinical populations. For example, Rubin (2011), Hoyt & Yeater (2011), Guastella & Dadds (2006), and Andrea et al. (2012) recruited from undergraduate samples; Lorenz & Meston (2012), Jelinek et al. (2010), and Papini et al. (2014) recruited through public advertisement; Manne (2002), Graves et al. (2005), and Owen et al. (2006) recruited through cancer medical centres. Alvarez-Conrad et al. (2001) and Booker et al. (2018) recruited through trauma centres; Wardecker et al. (2017) recruited sexual abuse victims through criminal case file records and Eid et al. (2005) recruited through a military training sample. There were no trends observed that were unique to certain samples, for example, particular linguistic markers for healthy volunteers versus those recruited through trauma centres. Studies using non-clinical samples [e.g. Hoyt & Yeater (2011), Guastella & Dadds (2006)] acknowledged that healthy participants may have had access to a greater variety of emotions and to associated narratives when describing personal critical life events, even with current emotional impact. It could also be assumed that healthy individuals use more cognitive strategies when reporting their emotional states

about a life event with high levels of current emotional impact (Rullkoetter et al. 2008).

3.21 Psychological processes

Within the psychological process category, affective dimensions (positive and negative words) were found to be the most prominent features of trauma narratives. Support for affective dimensions of trauma narratives were found in 15/16 studies included in the review. These studies consistently found more frequent use of affective words (positive and negative) within experimental groups.

Studies investigating biological process indicators found significant findings for increased use of sensory details or body words. Of the cognitive mechanisms category, strongest support was found for use of insight (e.g. think, know, consider) and causation/cognitive mechanism language (e.g. realize, understand, should). However, a number of studies investigated cognitive mechanisms within trauma narratives and found limited or no evidence supporting this variable (e.g. Graves et al. 2004; Papini et al. 2015; Rubin, 2011).

3.22 Linguistic processes and personal concern processes

When linguistic processes were examined, findings (Lorenz & Meston, 2012; Andrea et al., 2012; Papini et al., 2015) suggest that trauma narratives include greater use of first person pronouns (e.g. I, me, mine) and over use of the present tense. This finding was consistent across samples (childhood sexual abuse versus no childhood sexual

abuse; trauma narratives following 9/11; trauma + PTSD versus trauma + no PTSD). The LIWC 'personal concern' category refers to work, achievement, leisure, home, money, religion and death. Ng et al. (2015) and Papini et al. (2015) found strong support for the use of words relating to death (e.g. 'lethal, 'kill') in trauma narratives. This finding is likely, in part, to reflect the nature of the participants used in the studies. Ng et al. (2015) investigated trauma narratives of genocide survivors and Papini et al. (2015) included participants in their experimental group who were exposed to trauma who went on to develop PTSD. Guastella & Dadds (2006) found in their RCT comparing an emotional writing intervention versus a non-emotional writing task that trauma narratives included greater use of negative emotion words, over use of the present tense, physical body descriptors and motion descriptors (e.g. 'arrive' or 'go').

4.0 Discussion

The results of this review suggest that trauma narratives relative to non-traumatic narratives tend contain an abundance of affective and sensory descriptors, as assessed using the LIWC program. Results concerning cognitive mechanisms were more mixed with some studies finding support for increased use of insight and causation language (e.g. Hoyt & Yeater, 2011; Andrea et al. 2012; Booker et al. 2018) and others finding limited/no evidence to support this finding (e.g. Graves et al. 2004; Papini et al. 2015; Rubin, 2011). Whilst this reflects the overall trend of findings, we note that there was a lot of methodological variation across studies. For example, differences were found across the type and number of variables examined (e.g. some looked exclusively at affective variables, others focused on cognitive variables). Similarly, comparison

groups varied (e.g. PTSD versus no PTSD; severe trauma versus less severe trauma) as well as the nature and degree of trauma experienced.

The results of this review are consistent with other reviews of trauma narratives. For example, O’Kearney & Perrott (2006) found that findings across studies could be broadly categorised into information regarding (a) sensory/perceptual and emotional language or conceptual/cognitive words (i.e., words indicating causal and insightful thinking); (b) narrative disorganization or fragmentation; (c) disruptive temporal context (i.e. use of present tense); and (d) nature of references to self. The authors concluded that traumatic narratives were dominated by sensory/perceptual/emotional words. Similarly, Crespo & Fernández-Lansac (2016) found in their review that trauma narratives were dominated by sensorial/perceptual aspects when compared with narratives of other life experiences and that sensory details were related to posttraumatic symptoms. Sensory aspects were more frequently associated with dissociation and descriptions of flashbacks. This finding is consistent with the idea that deficits in encoding facilitate involuntary memories, which are rich in sensory and emotional content (Brewin et al., 1996; Ehlers & Clark, 2000). Specifically, dual representation theory of PTSD (Brewin, Dalgleish & Joseph, 1996) proposes that during trauma, the encoding of contextualised episodic memories is weakened, whereas the encoding of perceptual memories is strengthened. Therefore, individuals are able to deliberately retrieve contextualised representations, but reminders of the trauma also lead to automatic retrieval of perceptual representations, with a sense of reliving the event (Brewin, 2014; Booker et al., 2018). Alternatively, Rubin et al., (2008) propose that increased sensory and emotional content is not explained by different memory systems but by increased memory availability. This is due to

emotional events being more central to one's life history and therefore more rehearsed (Rubin et al., 2008). As in the current review, previous research has found mixed and often contradictory support for cognitive outcomes. For example Rubin (2011) and Porter & Birt (2001) found that trauma memories are not incoherent compared to non-traumatic memories.

4.1 Psychological processes

The current review supports the finding that evaluating the linguistic markers of trauma narratives can provide important insight into a victim's psychological state and potentially predict later symptomology (Marshall, 2016; Gray & Lombardo, 2001; Ng et al., 2015). Within the three broad psychological processes examined (i.e. biological, cognitive and emotional) specific linguistic markers have been determined to be associated with general PTSD symptom severity. This includes greater use of emotion words, pronoun use, faults in using the past tense and cognitive process words.

The current review found that greater use of body words (e.g., ache, heart), a subcategory of somatosensory detail, was positively associated with trauma severity (Lorenz & Meston, 2012; Guastella & Dadds, 2006; Ng et al., 2015; Rubin, 2011). One explanation for these findings is that sensory detail in trauma narratives bring about the intrusive, distressing memories typical in PTSD (Ehlers & Clark, 2000; Greenhoot et al., 2013; Marshall, 2016). Using sensory detail to describe trauma may be indicative, to some extent, of psychological re-experiencing at that time of recall (Marshall, 2016). It has also been suggested that narratives dominated by sensory words rather than cognitive process words are associated with greater symptomology

because the individual has been unable to make sense of the trauma, therefore using somatosensory details rather than causal and insight words to describe the event (Ehlers & Clark, 2000).

However, other studies, including a meta-analysis conducted by O’Kearney & Perrott (2006) found that affect words in general (including positive as well as negative words) were prominent within narratives produced by individuals suffering from PTSD. Similarly, Jaeger et al., (2014) reported that in female assault survivors, increased use of both positive and negative emotion words was related to PTSD symptoms. Considering these findings as a whole might suggest an increased use of positive words found in trauma narratives could be evidence of positive impression management (Marshall, 2016). For example, an attempt to convey to the interviewer an image of robustness or that they were not distressed by the trauma, something the authors argue might be more likely in a younger population. Zieba et al., (2019) note that a growing number of studies indicate that having to cope with trauma can result in post-traumatic growth (PTG) (Tedeschi and Calhoun, 2004; Calhoun and Tedeschi, 2006, Joseph and Linley, 2008; Calhoun and Tedeschi, 2013). PTG refers to positive psychological change experienced as a result of psychological challenge in order to rise to a higher level of functioning (Zieba et al., 2019). Research into PTG has typically consisted of using questionnaires to measure positive changes that may result from trauma, with response options ranging from “no change” to “significant change” (Zieba et al., 2019). It is possible that studies included in the current review that found an increase in the use of positive emotion words demonstrate support for the post-traumatic growth theory.

4.2 Linguistic processes

Clinical studies have found that during the initial stage of treatment for chronic PTSD, narrative accounts of trauma are characterized by “an abundance of speech fillers, repetitions, incomplete sentences, disorientation of time and space, and general confusion” (Alvarez-Conrad, Zoellner, & Foa, 2001, p. 160). However, there is considerable debate about the relationship between traumatic memories and cognitive narrative characteristics (Goldfine, 2010). Some researchers have found that traumatised individuals will provide shorter narratives (e.g. van der Kolk & Fisler, 1995). Beaudreau (2007) hypothesised that short trauma narratives may reflect the use of avoidance or be indicative of an idiosyncratic storytelling style. Other researchers speculate that greater arousal, salience, and rehearsal will result in longer or more detailed trauma narratives compared to narratives of non-traumatic events (Goldfine, 2010). Studies of non-clinical populations consistently support this hypothesis (Thompson, Morton & Fraser, 1997; Gray & Lombardo, 2001; Pennebaker, Kiecolt-Glaser & Glaser, 1988; Porter & Birt, 2001).

The results of the current review suggest that that trauma narratives often involve a confused sense of time (Jelinek et al., 2010; Guastella & Dadds, 2006; Manne, 2002; Booker et al., 2018; Waters et al., 2013). Specifically, these studies found that individuals recalling traumatic events tended to spontaneously shift from past to present tense. Moreover, Manne (2002) found that a greater use of past-tense words was associated with fewer PTSD symptoms. This is consistent with dual representation theory and Ehlers & Clark’s research into flashback memories which

have been found to contain significantly more present-tense verbs relative to non-flashback memories (Hellowell & Brewin, 2004; Goldfine, 2010).

4.3 Summary

The current findings demonstrate that specific LIWC variables were related to trauma symptomology. Specifically, findings indicated that in particular, positive, negative, sensory/body words, word count, insight, cognitive mechanism language, faults in using the present tense were positively associated with trauma narratives.

Analysing trauma narratives enables us to understand the memory disturbances linked to PTSD and thus to develop increasingly effective psychological interventions to promote trauma adaptation (Booker et al., 2018). The results of this review support the view that more consistent research using similar experimental and control groups is needed to better understand the relationship between affective and cognitive mechanisms of trauma narratives.

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Part 2. Empirical Research Paper

Recall of ‘trauma-related’ events following nitrous oxide: linguistic and psychophysiological correlates of recall.

1.0 Abstract

Background

Investigations into trauma narratives have consistently confirmed that PTSD is associated with deficits in verbal memory, as well as over general autobiographical memory, avoidance or suppression of memories, and negative interpretation of memory symptoms. In addition, memories for the traumatic event itself are typically seen as altered in two distinct ways: there is impairment in the voluntary retrieval coupled with increased involuntary memory, experienced as a dissociative alteration to sense of time. Early pharmacological interventions have been found to hold some promise in reducing the emergence of PTSD symptoms, possibly by preventing or reducing initial consolidation of traumatic memories. Clinical findings support the utility of novel pharmacological tools targeting NMDA receptor subunits (such as ketamine). NMDA receptors play an important role in memory reconsolidation. Using existing data, the current study sought to extend a recently published study on nitrous oxide (N₂O) and involuntary emotional memories using the ‘trauma video’ paradigm. It did this by investigating the relationship between N₂O inhalation and the declarative recall of ‘traumatic’ events, together with differences in sympathetic/parasympathetic activity during encoding and recall. In addition, the linguistic content of recalled events was analysed. The latter included potential linguistic markers of trauma (negative affect, insight, cause, analytic, authentic, pronoun) and the role of physiological changes (heart rate variability) during recall. This is the only study describing the effects of N₂O on declarative and psychophysiological aspects of emotional memory, which may have implications for the treatment and prevention of PTSD.

Method

Participants were randomized to inhale N₂O (N = 25) or medical air (N = 25) after viewing a negatively valenced emotional film clip ('trauma film') while cardiac activity was monitored. A week later, participants completed an explicit memory recall task related to the film.

Results

Results of the study did not find significant group differences between the N₂O group and placebo group on emotional memory. Specifically, the study found that N₂O did impair declarative memory and contrary to hypotheses, did not decrease narrative cohesion and self-focus. The study found that baseline HRV was correlated with voluntary memory performance in the N₂O group only, but not involuntary memory.

Conclusions

Despite impairment in involuntary emotional memory, N₂O does not appear to degrade declarative memory. Since the latter is required for contextualisation of trauma memories, this finding suggests that N₂O's beneficial effects on trauma memory are not counteracted by impairment in 'verbally accessible' memory of the traumatic memory (the main technique of exposure-based psychotherapy for PTSD). Accordingly, further research is needed to continue investigating ways of detecting emotional arousal (e.g. fear and perceived threat) and different states of consciousness such as depersonalisation, derealisation, and flashbacks during voluntary recall of trauma among individuals with PTSD.

2.0 Introduction

Posttraumatic stress disorder (PTSD) can be characterised as a prolonged maladaptive response to a traumatic event (Cox & Olatunji, 2017). Memory impairment is a core feature of PTSD (Amir, Badour & Freese, 2009). For example, diagnostic symptoms include intrusive thoughts, flashbacks, and fragmented recall of the traumatic experience (DSM-IV, American Psychiatric Association, 2000) and may all be associated with deficits in the formation of autobiographical memory. According to the National Institute for Health and Care Excellence (NICE) guidelines around 25–30% of people experiencing a traumatic event may go on to develop PTSD (NICE, 2005).

In addition to trauma-specific symptoms, research suggests that individuals with PTSD also experience broader, more general cognitive disruptions, such as difficulties concentrating and memory for non-trauma-related information (Wolfe & Charney, 1991). Similarly, it has been widely documented that individuals with PTSD score lower than matched controls on neuropsychological tests of various memory constructs (see Brewin, Kleiner, Vasterling, & Field, 2007). This includes acquiring or learning new information, sensitivity to retroactive interference and delayed recall of information (Amir, Badour & Freese, 2009).

2.1 Dual Representation Theory

The dual representation theory (Brewin, Dalgleish & Joseph, 1996) of PTSD assumes that two different types of memory representation are encoded at the time of the

traumatic event. One type of representation consists of sensory, affective details and the other includes a contextual representation (Brewin & Burgess, 2014). In healthy memory, the sensory and contextual representations are tightly associated, whereby sensory information is typically retrieved through contextual representation and access to contextual data is under voluntary control (contextual representation or C-rep for short). However, dual representation theory proposes that extreme affective salience experienced during traumatic events result in sensory representation being involuntarily activated (sensory-bound representation or S-rep for short). The information remains isolated in the S-rep system and, when triggered, there are no corresponding C-rep memories to tell the brain the danger is past and inhibit the fear response (Brewin, 2003). This causes re-experiencing in which the emotions that were present at the time of the trauma appear to be re-created with their original intensity (Bisson, 2009). Simultaneously the contextual representation is either encoded weakly or without the usual tight association to the sensory representation (Brewin & Burgess, 2014). This can be attributed to a dissociative response to stress-induced trauma reaction and/or the down-regulation of the hippocampal memory system (Jacobs & Nadel, 1985).

Brewin et al. (1996) suggest that successful emotional processing is a largely conscious process dependent on S-reps to aid cognitive readjustment by supplying accurate sensory and physiological information about the event. S-reps allow for active, conscious attempts to make sense of the trauma, and integrate this information with pre-existing schemas about the world (Bisson, 2009). Following traumatic events Brewin et al. (1996) argue that there are 3 potential outcomes of emotional processing:

(1) coherent, well integrated emotional processing (2) pathological chronic emotional processing (3) premature inhibition of processing.

2.2 Emotional Memory and arousal in PTSD

In PTSD, memory networks representing information about threat become highly elaborated and accessible, affecting the individual's capacity to voluntarily encode and retrieve information (Hayes, Van Elzaker & Shin, 2012). Emotional processing theory (Foa & Kozak, 1986; Foa & Rothbaum, 1998) proposes that trauma related events stimulate the development of an extensive fear network in memory. This includes information regarding the feared situation, responses to it, and interpretive meanings of the two. The fear network generated is over-inclusive and pervasive resulting in originally unrelated trauma-stimuli (both internal and environmental) triggering arousal and re-experiencing symptoms now associated the traumatic event. As a consequence, the persistence of these interfering symptoms is seen as a hallmark of PTSD; the inappropriate associative representations giving rise to arousal and subsequent avoidance (Amir, Badour & Freese, 2009).

Neurotransmitters and neurosteroids including norepinephrine and cortisol play a critical role in the fear and stress response by mobilizing the body's response to the stressor, for example, via the hypothalamus-pituitary-adrenal axis (HPA) and amygdala (Hayes et al. 2012). Norepinephrine has been shown to facilitate emotional memory (Ferry et al., 1999). Despite this finding however, the literature suggests that emotional memory may not be uniformly enhanced during high levels of arousal. For example, "tunnel memory" (Easterbrook, 1959) refers to a narrowing of attention

following exposure to negative, highly arousing material. This results in key, central features of a scene being better consolidated than peripheral information in the background.

Studies exploring the neural underpinnings of emotion and memory highlight in particular the interactions between the amygdala and hippocampus. The modulation hypothesis proposes that the amygdala's influence on other medial temporal lobe structures including the hippocampus results in emotionally salient experiences being better remembered than neutral events (McGaugh et al., 1996). The modulation hypothesis has been supported by use of fMRI scans which have demonstrated greater hippocampal and amygdala activity for correctly recalled words over forgotten emotional memories (Dolcos et al., 2004).

2.3 Autonomic changes in PTSD

Studies investigating physiological markers following exposure to a trauma event have found increased sensitivity to a range of affective responses including reduced heart rate variability (HRV) (Liddell et al. 2016), which is increasingly accepted as a physiological correlate of impaired emotion regulation. The persistent state of hyperarousal that characterizes PTSD suggests autonomic dysregulation; in particular, downregulation of parasympathetic nervous system (PNS) and an elevated sympathetic nervous system (SNS) activity (Blechert, Michael, Grossman, Lajtman, & Wilhelm, 2007). Because heart rate is regulated by both PNS and SNS, heart rate increases could be due to increased sympathetic activity, attenuated parasympathetic activity, or both (Pole, 2007; Tan, Wang & Ginsberg, 2013). Such physiology reflects

altered vagal nerve function (Porges, 2011) and impaired emotion regulation capacity (Appelhans, & Luecken, 2006). HRV has gained research attention due to its ability to provide separate estimates of PNS and SNS activity (Chou et al., 2018). Applying frequency domain analysis (Cohen et al., 1999) the high frequency component of HRV (HF-HRV) is considered as a marker of PNS activity. The low frequency component (LF-HRV) is suggested to be a marker of SNS activity (REF). Consequently, some believe the LF/HF ratio reflects SNS/PNS balance, and others believe it indexes SNS activity (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Another time-domain parameter is the root mean square of the successive differences (RMSSD). RMSSD is correlated with high-frequency power (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). RMSSD and high-frequency power have been widely used as measures of HRV in several previous studies (DeGiorgio et al. 2010; Koenig et al. 2015; Koenig et al. 2016).

In response to a salient external cue, such as a threat signal, the so called ‘vagal brake’ is released, allowing the sympathetic nervous system to dominate and mobilize defence responses (Porges, 2011). A higher level of resting-state HRV is associated with healthy emotion regulation capacity (Appelhans, & Luecken, 2006; Quintana et al., 2012), indicating a system that is able to effectively respond to environmental challenges and restore homeostasis after a threatening experience (Liddell, 2016). This includes psychological flexibility and emotional self-regulation (Porges, 2011; Thayer & Lane, 2000). Alternatively, low resting state HRV, in addition to dominance of SNS activity, is associated with greater psychophysiological rigidity evidenced through reduced ability to regulate emotional responses following distressing events

(Appelhans, & Luecken, 2006). This finding has been replicated within studies investigating the relationship between reduced resting HRV and PTSD (Lakusic et al. 2007); depression and anxiety (Kemp et al., 2010, 2012; Chalmers et al. 2014); aggression and anger (Vogele et al., 2010); comorbidity (Kemp et al., 2010, 2012), and poor physical health (Kemp & Quintana, 2013). Studies have also linked reduced resting HRV with increased vulnerability to distress (Shaikh al arab et al. 2012) and delayed physiological recovery following stress exposure (Weber et al., 2010).

Review of existing published research suggests that HRV biofeedback seems promising as a treatment for PTSD. For example, through both reducing symptoms of PTSD and improving cognition (For review see Liddell, 2016). Drop-out rates have been found to be low, HRV interventions can be used as a simple, non-invasive indicator of the autonomic nervous system (Sztajzel, 2004), there is the potential for individuals suffering from PTSD to benefit from HRV interventions, such as HRV biofeedback. Such interventions are both portable and relatively inexpensive. As such, HRV is both a diagnostic variable as well as forming the basis of treatments that are potentially a viable alternative to traditional treatment such as prolonged exposure therapy, cognitive behaviour therapy and cognitive processing therapy. Despite these initial findings however, larger-scale and rigorous controlled trials are needed to confirm such positive outcomes.

Although there is some limited research on HRV and emotional memory, the influence of HRV during encoding on subsequent emotional memory performance is not well established (although several studies have shown an association between heart *rate* and subsequent memory). It is possible that initial memory formation (consolidation)

supported by especially high sympathetic activity (low HRV) during encoding (Blechert et al. 2007) can be reversed by consolidation interfering treatments.

2.4 Linguistic aspects of emotional/trauma memory

Studies exploring trauma narratives suggest that structural (e.g. disorganisation and fragmentation) and content-related (e.g. emotion words such as “afraid”, cognitive processing words such as “because” and use of pronouns, such as “I” or “we”) aspects of trauma narratives may be associated with the development of PTSD (Jaeger et al. 2014; Byrne, Hyman & Scott, 2001; Porter & Birt, 2001).

Studies of *structural* features of the trauma narrative suggest difficulties accessing particular details of the event, the presence of speech filters or repetition and confusion regarding temporal order or elaborating the trauma memory (Ehlers & Clark, 2000; van der Kolk & Fisler, 1995). Investigations into the *content* features of trauma narratives have shown that individuals with trauma related psychopathology use a greater number of emotion words with greater intensity than those with non-trauma autobiographical narratives (Porter & Birt, 2001; Byrne, Hyman & Scott, 2001). Studies in this field also show that the presence of non-self-referential pronouns is related to poorer functioning (Klein & Janoff-Bulman, 1996) whilst the use of cognitive processing words is related to better functioning (Alvarez-Conrad, Zoellner & Foa, 2001). Other linguistic markers of trauma/ trauma vulnerability have been explored using a variety of linguistic-analytic methods.

For example, the Linguistic Inquiry and Word Count (LIWC) (Pennebaker et al., 2007) software was developed to provide an effective method for studying the various emotional, cognitive, and structural components of verbal and written speech. LIWC has been used within the PTSD literature (e.g. van Minnen et al., 2002 & Jaeger et al. 2014) when examining trauma narratives. For example, Jaeger et al. (2014) found that the content of trauma narratives rather than the structural aspects of the narrative (i.e. the specific words descriptors used rather than the relationship between them) may be more strongly associated with trauma related reactions. This finding is in keeping with PTSD treatment trials which have failed to find changes of trauma narrative fragmentation associated with recovery rates (van Minnen et al., 2002). The authors concluded therefore that narrative recounting was consistent across a range of treatment modalities such as narrative exposure therapy and exposure based therapies should perhaps be prioritising increasing emotional engagement through emotion words and reducing negative self-focus and trauma related guilt rather than focusing on decreasing fragmentation and increasing organisation. However, Jaeger et al. (2014) called for greater investigation into trauma narratives (both structural and content related) so to better inform trauma related treatment. While it seems likely that verbally-based treatments, e.g. cognitive therapy, will affect verbal representations of a trauma (e.g. through formation of new cognitive representations of the event), it is unclear whether non-verbal treatments, particularly biological/pharmacological treatments, would affect the quality of trauma narratives.

2.5 Consolidation of emotional memory and its modulation

Preventing the development of maladaptive trauma memories, for example, by using secondary prevention strategies shortly after the traumatic event, is clearly preferable to treatment of PTSD, which can have a chronic course (Das, Tamman, Nikolova et al., 2016). The research in the area of early intervention has typically focused on the use of cognitive-behavioural procedures following trauma. However, experimental studies have also examined the impact on occurrence of intrusive memories of a visuospatially demanding task (Tetris) following viewing aversive video footage (an experimental model of PTSD). These studies have suggested that the number of intrusive memories reduced when they engaged in the task (Holmes et al. 2009, 2010), an effect which might be mediated through reduced memory consolidation.

An alternative approach is to attempt to prevent the development and strengthening of maladaptive memory traces by interfering with their consolidation pharmacologically. This approach draws upon the understanding that long-term potentiation (LTP) is the molecular basis of memory consolidation (Jones et al. 2001; Bliss & Collingridge, 1993). Therefore, interventions that inhibit LTP may prevent consolidation of traumatic memory (Das et al. 2016).

Critically late LTP, which is thought to reflect memory consolidation, is dependent on activation of the N-Methyl D-Aspartate receptor (NMDAR). The NMDAR system has been implicated in synaptic plasticity, and learning and memory across a range of memory systems, thereby likely contributing to consolidation of trauma memories in PTSD (Sherin & Nemeroff, 2011). Further support for this theory is derived from

experiments in which pre-treatment with a glutamatergic NMDA-receptor antagonist was seen to decrease stress responsiveness as measured by adrenocorticotrophic releasing hormone (ACTH) release (Jezova et al., 1995; Tokarev and Jezova, 1997). This suggests that changes in glutamate levels play a key role in initiation and maintenance of the HPA response (Ravindran & Stein, 2009). Further, Ravindran & Stein (2009) suggest that following traumatic events, elevated glutamate levels may not only serve to encode and consolidate traumatic memories, but also enhance hippocampal damage. In keeping with this Das et al. (2016) suggested that post-trauma NMDAR antagonism may prevent the consolidation of long-term maladaptive memory traces, reducing PTSD symptomatology.

Early pharmacological interventions have been found to hold some promise in reducing the emergence of PTSD symptoms, possibly by preventing or reducing initial consolidation of traumatic memories (Horn, Charney & Feder, 2016). Human studies of pharmacological agents administered shortly after trauma exposure have included studies testing the efficacy of high-dose glucocorticoid immediately following trauma exposure (Surís et al., 2010; Zohar et al., 2011). Zohar et al. (2011) highlight the significance of “golden hours”, i.e. focusing on a defined and limited “window of opportunity” namely the first 6 hours after the trauma exposure in order to effectively consolidate trauma memory. For example, McGhee et al. (2008) found that in a group of burned service men those treated with the NMDA receptor antagonist ketamine during hospitalization had lower incidence of PTSD. Such clinical findings support the utility of novel pharmacological tools targeting NMDA receptor subunits or function could be of benefit while avoiding some of the side effects inherent to NMDA receptor blockade (Steckler & Risbrough, 2012). NMDA receptors also play an

important role in reconsolidation processes (Suzuki et al., 2004; Lee et al., 2006) and it can be suggested that manipulations that attenuate NMDA receptor function may also be of benefit (Steckler & Risbrough, 2012).

While studies using ketamine are promising, ketamine is a difficult compound to use clinically. Generally, it is used as a dissociative anaesthetic and needs to be administered intravenously. It produces marked psychotomimetic and dissociative reactions which can be highly unpleasant (Steckler & Risbrough, 2012), potentially limiting its wide use in psychiatry. On the other hand, nitrous oxide (N₂O), another NMDA antagonist, produces similar, though milder, psychological effects, its unique pharmacokinetic profile means that any negative reactions quickly reverse (within minutes of terminating inhalation). It is also a uniquely safe drug used widely in prenatal and paediatric care. As such, a fuller description of its neuro-pharmacological profile (e.g. in terms of its effects on emotional memory) is long overdue. For example, while the preliminary effects reported by Das et al are consistent with an NMDAR mediated reduction in consolidation of 'trauma-related' memory, N₂O's effects on declarative aspects of such emotional memories remains unclear.

Das et al. (2016) based their conclusion on the potential clinical utility of N₂O on the observed reduction in frequency of traumatic intrusions in participants who viewed a trauma video. N₂O is well tolerated, can be administered very easily and has rapid onset and offset kinetics. As such, it is a widely used pre-hospital analgesic used by emergency and surgical services (Hoeffe, Trottier, Bailey, et al. 2017). Das et al's findings might suggest that it could also potentially be used as a first-line (secondary) preventive treatment in the aftermath of trauma.

Although a number of drugs have been trialed as potential secondary prevention strategies (e.g. propranolol and hydrocortisone) Das et al's (2016) study is the only one to examine N₂O (Das et al, 2016). However, these authors focused primarily on intrusive memories and did not examine the full range of emotional memory performance. Indeed the effects of N₂O on declarative memory in humans is very limited. Such investigation is required in order to fully assess N₂O's therapeutic and harmful potential.

2.6 The present study

The current study used unanalysed raw data from the Das et al. (2016) study investigating the potential interfering effects of N₂O on *involuntary* memories. Although these authors recorded declarative memory using a free recall task one week after the simulated trauma, due to the absence of a scoring frame for the complex and multifaceted trauma video used in that study, that data was not examined. The current study therefore involved developing a scoring system for the trauma video to allow the effects of N₂O versus medical air on the *declarative recall* of the trauma film to be investigated. In addition, the linguistic content of the recalled narrative and the role of physiological changes (heart rate variability) *during encoding* on subsequent memory performance were examined. It is necessary to understand its impact on declarative recall to determine whether participants are still able to maintain (form and consolidate) a *coherent* declarative memory, which is considered to be necessary for a properly contextualised representation of sensory aspects of memory, and which therefore reduces the tendency for sensory representations in the form of involuntary

memories to dominate retrieval. In the case of N₂O, it remains unclear whether N₂O its effects are specific to sensory memories or if it causes a more global amnesia. The current study also assessed the *quality* of the recalled narrative.

2.6.1 Research aims

The aim of the current study was to investigate the relationship between N₂O and the declarative recall of traumatic events. In particular, it addressed two primary research questions:

- (1) does N₂O inhalation improve the recall of traumatic memories and does this depend on whether the recalled material relates to gist *versus* detail of the memory?
- (2) Due to its dissociative effects, does N₂O decrease narrative cohesion and self-focus in terms of the content of retrieved memories?
- (3) An additional, exploratory question related to whether there was an association between low levels of HRV (sympathetic dominance) at encoding and subsequent recall and whether this association was dependent on group (i.e. was the association only seen in the medical air group?).

These primary research questions were addressed through:

1. Developing a memory scoring frame and scoring system for free recall data in terms of idea units of gist and detail (Cahill et al. 2004). Gist in this context refers to “the main events of a situation...“central” information...any information that cannot be removed or altered without changing the

fundamental story line” (Cahill et al. 2004, p. 392-393) whereas detail refers to the “peripheral information” (Cahill et al. 2004, p. 392).

2. Using LIWC to examine linguistic aspects of recall. Specifically, affective features (i.e. negative emotion words) and cognitive features (i.e. cognitive mechanisms, insight and cause words (Rubin et al. 2016).
3. Using Kubios to examine HRV within specific trauma scenes of the two video clips. This data was used to compare group differences (N₂O versus medical air), idea units (gist/detail) and LIWC variables.

As the study aims were to investigate the relevant relationships outlined above, no specific directional hypotheses are presented due to the exploratory nature of the study.

2.6.2 A note on the use of existing data and extending the previous (Das et al, 2016) study

While this study did not involve any new data collection, it represents a significant extension of the previous work in the following ways (which will be further elaborated in the methods section below).

- 1) Development and applying a scoring system (for the first time) to the trauma video free recall task.
- 2) Subjecting the recalled narratives of participants to the linguistic analysis programme, LIWC
- 3) Retrospectively identifying sections of psychophysiological (electrocardiogram) recordings during encoding of the trauma video that were

later recalled (a ECG version of the more commonly described EEG-based ‘subsequent memory effect’) for each recalled idea unit, for each participant.

3.0 Method

As noted above, this study did not involve new data collection. Details of the protocol used in Das et al. (2016) are provided below with additional specific methodological details elaborated upon where these are novel and developed for the current study.

3.1 Participants

The participants were fifty two adults (28 male, 24 female), aged 18-65 with normal physical health and normal or corrected to normal colour vision. See table 1 for sample baseline characteristics. All procedures were approved by the UCL research ethics committee (ethics approval ID: 3901/001).

Table 1. Sample baseline characteristics

	N2O group	Medical air group
Participants	26	26
Male	13	15
Female	13	11

3.2 Eligibility Criteria

Adults with normal physical health and normal or corrected to normal colour vision. Exclusion criteria included self-reported historical or current diagnosis of mental

health issues; a history of trauma, memory impairments, pregnancy or breast-feeding, regular (>1 times per month) recreational use of drugs other than alcohol and caffeine (including N₂O or other NMDAR antagonists), vitamin B12 deficiency and pneumothorax.

3.3 Design

Participants were randomised to inhale N₂O (N = 26) or medical air (N = 26) after viewing a negatively valenced emotional film clip ('trauma film'). One week later, participants completed an explicit memory recall task related to the film.

3.4 Trauma film

The emotional video consisted of two clips taken from the film 'Irreversible' (Studio Canal, France). The scenes depicted a violent sexual assault (scene 1, 15 min long) and a man being beaten to death in a club (scene 2, 4 min long). The use of these clips was based on pilot data showing a greater number of intrusions following this clip than previously used multiple short scenes (Soni et al. 2013).

3.5 Subjective assessments

To assess levels of dissociation, the Clinical Administered Dissociative States Scale (CADSS; Bremner et al. 1998) was used. The Beck Depression Inventory (BDI; Beck et al. 1988) was used to assess levels of depression, the Distress Tolerance Scale (DTS; Simons & Gaher, 2005) to assess participants' individual capacity for managing

distressing experiences and the Dissociative Experiences Scale (DES) as assess naturalistic levels of dissociation (Carlson & Putnam, 1993). Acute emotional responses to the film were assessed with a set of six visual analogue scales (VAS) measuring levels of disgust, fear, anger, sadness, happiness and distress assessed on a scale of 1-10. These were anchored with the descriptors ‘not at all’ and ‘extremely’. A single-item VAS was also used to assess drug-induced nausea.

3.6 Memory assessment

For the current study, memory was assessed at a single time point one week after viewing the trauma film. The dataset consisted of each participant’s raw prose recall for each of the scenes. A preliminary aspect of this project involved developing a memory scoring for the free recall of data gathered during the recall task. This involved reviewing free recall content from all participant in Das et al (2015), extracting ‘idea units’. For example, developing a system to code all the data (units of memory). A single aggregate recall score (number of declarative ‘idea units’) was determined for each participant. Each idea unit was a self-contained detail or gist element of the scenes. Whether a recalled aspect was classified as ‘gist’ or ‘detail’ was based on the definitions used by Chou et al. (2014). Namely, ‘gist’ memory referred to the contextual details of the scene (e.g. when, where, how, who) and the ‘detail’ memory referred to sensory elements in the scene (e.g. the colour of the dress that the victim wore). The recalled prose was split into individual idea units. The boundaries and classification (as gist or detail) of each unit was determined by the authors.

Identification of the gist and detail information contained in the scenes were carried out prior to examining participant data. A preliminary memory scoring frame was developed through viewing the videos based on standard gist definitions prior to examining the detail (Chou et al., 2014; Cahill et al., 2004). This initial frame was modified (expanded upon) by incorporating correct answers identified across all participants (verified by an independent rater). This was an adaptation of a methodology described in Bourne, Mackay & Holmes (2013) who used this approach to score unique flashback per participant as a proportion of all possible flashbacks based on themes identified across participants. In the current study we expressed recalled 'idea units' against all possible idea units identified by the researchers and across participants. Incorrect gist/detail information was recorded as "false" gist or detail. For example, incorrectly recalled information about an item of clothing would be labelled as 'false detail'. No existing recall template exists for the specific scenes from the irreversible videos used in the study by Das et al (2016). Therefore developing a frame for the video clips is unique to this study.

Following completion of the scoring frame, specific trauma events within the videos were determined. The collapsing of the individual idea units into trauma events were then analysed in relation to heart rate activity.

3.7 Language characteristics of 'trauma memory'

LIWC was used to provide a comprehensive linguistic assessment of the recall data. LIWC has been widely used in studying narratives of stressful and traumatic events and can produce up to 90 output variables for each text file. This includes summary

language variables (analytical thinking, authenticity, and emotional tone), standard linguistic dimensions (e.g., percentage of words in the text that are pronouns, articles, auxiliary verbs, etc.), word categories tapping psychological constructs (e.g., affect, cognition, biological processes, drives), informal language markers (assents, fillers, swear words), and punctuation categories (full stops, commas, etc).

Based on the literature outlined above, word categories tapping specific psychological constructs, namely affective (positive and negative emotion) and cognitive (cognitive mechanism language, insight words) elements were obtained for each participant's recall narrative. In keeping with previous trauma literature using LIWC (see chapter 1), which has shown the predictive value of specific linguistic variables, the present study focused on the following outcomes: word count, negative affect, insight and cause words, analytic words and pronoun (Rubin et al. 2016; Rubin, 2011; Rude, Gortner, Pennebaker, 2004).

It was anticipated that through using a combination of these procedures, a more robust and detailed understanding of trauma memory would be produced incorporating both language variables and contextual and sensory elements.

3.8 Heart rate variability (HRV)

The physiological data took the form of 'R-R' intervals recorded during a 5-min epoch prior to viewing the trauma film, during the entirety of the trauma film (peri-film) and 2 minutes following the film (post-trauma). These data were acquired using an ambulatory ECG device (see Das et al for details). Of note, data collected in the post-

trauma phase included gas inhalation (N₂O or medical air). The indices used to analyse heart rate variability included the Root Mean Square of the Successive Differences (RMSSD); this is the most common index of HRV recommended for short timescale recordings (REF). Data also used the ratio of the normalised proportion of high frequency and low-frequency band fluctuations in HRV, which is an indirect measure of the balance of parasympathetic : sympathetic activity (Chou et al., 2018). Heart rate data was imported into Kubios (Tarvainen et al. 2009) for Matlab (The MathWorks Inc., USA).

3.9 Drug administration

Drug was medical 50% N₂O in oxygen (Entonox) and was administered via an Ultraflow demand valve regulator (BPR Medical Ltd, UK). Participants in the placebo group were fitted with an inhalation mask connected a cylinder of medical air (British Oxygen Company) with transparent polyethylene tubing. Gas cylinders were not visible to participants in order to maintain the single blind. All participants inhaled the appropriate gas for 30 min in total.

3.10 Statistical Analysis Plan

All data was analysed using IBM Statistical Package for the Social Sciences (SPSS) version 22 for Windows (IBM Corp, USA). Outliers were identified as extreme values, exceeding 3 SDs from the mean. Such values (only a single such univariate outlier was identified) were windsorized to the mean for that variable +3 SD. In regression analyses multivariate outliers were identified using leverage values (Field, 2017).

When identified, the relevant analysis was conducted with and without the relevant data.

The key analyses consisted of mixed ANOVAs for drug effects (N₂O v medical air) on declarative/voluntary memory and repeated measures ANOVAs for time (peri- and post-‘trauma’ film) and HRV. Assumptions of normality and sphericity were met for the data. Regression analysis was performed to examine the relationship between gist memory and HRV and their interaction. Between-group (N₂O v medical air) comparisons, examining differences in emotionality, cohesion and self focus variables (based on a small number of LIWC variables), number of gist and detail ‘idea units’ for the free recall of data gathered during the recall task. These group differences were examined using ANCOVA where a moderating variable’s role was being examined.

3.11 Power calculation

A power analysis using the G power computer program (Faul et al., 2007) indicated that a total sample of 52 was needed to detect large effects ($d=.8$) with 80% power for a single between samples comparison with $\alpha =.05$ and power, 0.8. It is acknowledged however that the study was underpowered to detect smaller effects, and similarly other analyses.

4.0 Results

4.1 Drug effects (N₂O v medical air) on declarative/voluntary memory: gist and detail

Memory performance based on the newly developed memory scoring frame, was examined using a 2 x 2 mixed within-between ANOVA. Voluntary memory type (gist, detail) was the within subjects factor and drug (N₂O, placebo), the between subjects factor. This showed no main effect of group ($F(1,45)=0.008$, $p=0.928$) and no group x memory type interaction ($F(1,45)<0.001$, $p>0.99$). As expected, there was a main effect of memory type, such that significantly more detail was recalled than gist ($p<0.001$; Fig 1). Inclusion of neither pre- nor on-gas CADDs as covariates appreciably affected the main or interaction effects (F values < 1).

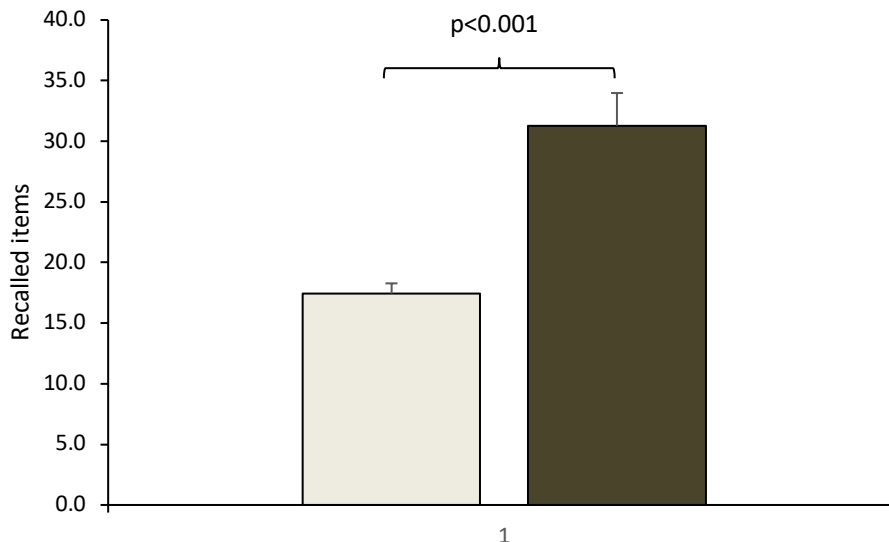


Figure 1: Main effect of memory type. Mean \pm standard error gist (light grey bar) and detail (dark grey) voluntary recall collapsed across drug (medical air and N₂O).

4.2 False voluntary memory

Since false gist recall showed floor effects (mean <1 false gist recall), a single total false recall score (gist+detail) was calculated for each participant. Since it was of interest to determine whether N₂O-induced dissociation might contribute to increased false recall at follow-up, 'on gas' CADDs scores were used as a covariate in the analysis of false memory.

ANCOVA showed that there was no difference ($F(1,43)=0.38, p=0.541$) in the number of falsely recalled gist/detail items when comparing medical air (Mean + SD: 3.00 ± 2.17) and N₂O (Mean ± SD: 2.52 ± 2.10).

4.3 Effects of drug on potential linguistic markers of trauma: Linguistic Inquiry and Word Count (LIWC)

The effects on potential linguistic markers with relevance to emotional memory recall are presented in Table 2.

Table 2. Medical air and N₂O group differences for linguistic markers of trauma recall

LIWC variable	Medical air (Mean + SD)	N ₂ O (Mean + SD)	t value (df)	p
Word count	246.61 + 77.90	231.44 + 95.81	-.599 (46)	.552
Negative affect	4.08 + 1.63	4.42 + 1.73	.695 (46)	.491
Insight	.86 + 1.05	.99 + 1.35	.384 (46)	.702
Cause	.46 + .45	.38 + .44	-.599 (46)	.552
Analytic	88.45 + 9.16	85.28 + 12.35	-1.002 (46)	.321
Authentic	23.49 + 17.85	22.65 + 22.05	-.145 (46)	.885
Pronoun	12.90 + 3.06	12.90 + 4.29	.007 (46)	.994
Body words	2.98 + 1.08	2.95 + 1.30	-.101 (46)	.920

Inclusion of dissociation (on gas CADDs) did not appreciably change any of the group effects outlined above (all p values from ANCOVAs >0.5).

4.4 Heart rate variability

Repeated measures (RM) ANOVA of HRV (RMSSD) showed a main effect of time ($F(2,74)=4.852$, $p=0.01$) but no main effect of group ($F(1,37)=0.77$, $p=0.386$) and no group x time interaction ($F(2, 74)=0.410$, $p=0.665$). The effect of time is shown in Figure 2 and as can be seen, there was a clear increase in HRV between peri- and post-‘trauma’ ($p=0.036$). Unfortunately however, since the post-film period also coincided with gas inhalation, it is not possible to disentangle effects reflecting spontaneous parasympathetic control/recovery following the film versus drug-related effects.

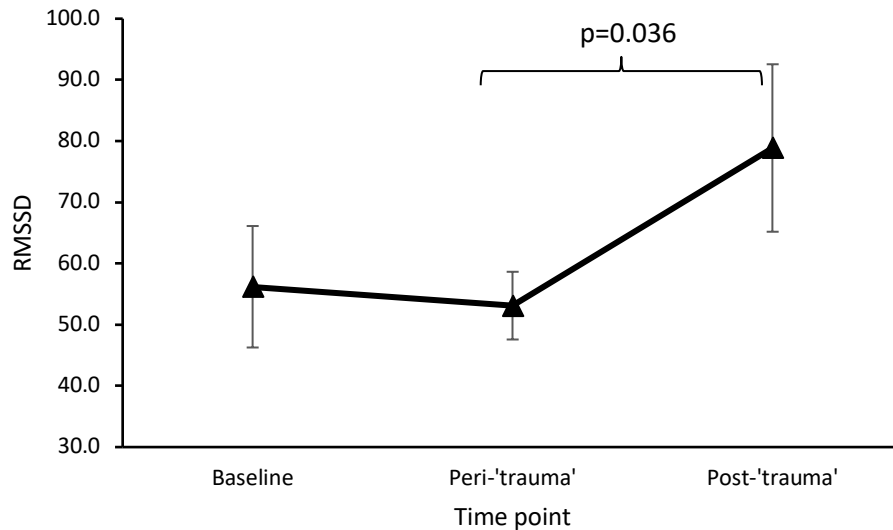


Figure 2. Mean \pm SEM heart rate variability (RMSSD) collapsed across drug groups at three time-points.

4.5 Relationship between heart rate variability and trauma-film memory

It was first of interest to examine the relationship between HRV (RMSSD) and the key memory variables: intrusive memories, and voluntary gist and detail memory.

Table 3 shows the correlation matrix for these variables.

Table 3. Correlation matrix for key memory variables and HRV (RMSSD)

	RMSSD (baseline)	Intrusions	Gist	Detail
RMSSD (baseline)	-	-0.027	0.312*	0.351**
RMSSD (trauma)		-0.057	0.223	0.194
Intrusions		-	-0.047	-0.011
Gist			-	0.358**

* P=0.053 **p<0.05

As is evident from table 3, baseline RMSSD was correlated with voluntary (but not involuntary) memory performance. There was no significant association between peri-trauma HRV and any of the memory indices: the amount of variance in gist or detail accounted for by peri-‘traumatic’ HRV (R^2) was more than five-fold lower relative to associations with baseline HRV.

It is also worth noting from table 3 that intrusions did not correlate with gist or detail memory, supporting the notion of separate/separable memory systems underlying sensory-intrusive and contextual/verbal-voluntary memories.

4.6 Baseline heart rate variability and gist memory

The association between gist and HRV was examined using multiple regression, including a Group x RMSSD interaction term to test for moderation by group, of the relationship between HRV and memory. Parameter estimates are displayed in table 4.

Table 4: Multiple regression, regressing gist memory on baseline HRV and the interaction between group and baseline HRV

Parameter	B	S.E	t	p
Intercept	17.642	1.473	11.98	<0.001
Group	-5.607	2.338	2.40	0.022
RMSSD	0.003	0.020	0.142	0.888
Group x RMSSD	0.080	0.032	2.500	0.017

The overall regression model was significant ($F=3.80$, $p=0.019$). As shown in table 4, there was an effect of Group and a Group x RMSSD interaction. Simple slopes

analyses are shown in Figure 3. This shows that while there was a positive association between RMSSD levels and gist memory ($R^2=0.404$) in the N₂O group, no such association as found in the placebo group¹. The inclusion of on-gas CADDSS score in the model did not appreciably affect the overall model ($p=0.047$), as the interaction remained significant ($p=0.026$).

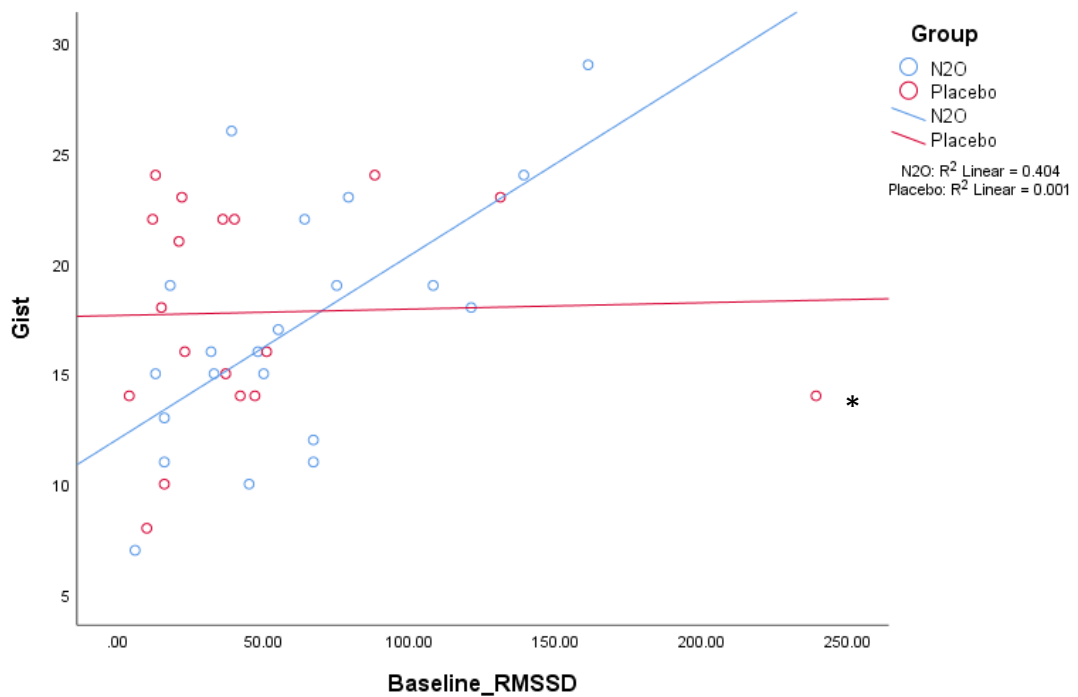


Figure 3. Simple slopes for N₂O and placebo. Note, removal of the datapoint marked by *, a multivariate outlier, resulted in a non-significant interaction (see footnote 1).

¹ Note, the data point with an RMSSD value of ~240 was originally an outlier but was windsorized to the current value (<3 SD from the mean) used in the analysis presented here. Removal of this data-point resulted in non-significant effects of group. However, since this value was not the result of a technical or data-input error, it was retained. Nonetheless, given the change in significance level with the removal of the datapoint, the interaction should be interpreted with caution, as the model may not be stable across samples.

4.7 Baseline heart rate variability and detail memory

The overall regression model using the same predictors in the analysis of detail memory was not significant ($F=1.726$, $p=0.18$). Neither the effect of group, nor the group x RMSSD interaction were significant ($p>0.5$).

4.8 Heart rate variability during trauma film – gist memory

The overall regression model using gist memory and HRV *during* the trauma film (i.e. during encoding) was also examined using multiple regression, using the same terms as used in the analysis involving baseline HRV. This model was not significant ($F=1.047$, $p=0.38$). Neither the effect of group, nor the group x RMSSD interaction were significant ($p>0.5$).

4.9 Relationship between linguistic markers and group controlling for dissociation and RMSSD at baseline

The association between key affective and cognitive LIWC variables and memory recall was examined using multiple regression, including a Group x RMSSD interaction term to test for moderation. None of the LIWC variables and gist memory were found to be significant. The models did not change significantly when controlling for RMSSD at baseline or dissociation (on-gas CADDIS score). The outcomes of these regressions are presented in table 4.

The overall regression models using gist memory and key linguistic variables (negative affect, insight, cause, analytic, authentic, pronoun) during the trauma film were examined using multiple regression, including a Group x CADDIS interaction to test for moderation. None of the models were found to be significant. Neither the effect of group, nor the Group x CADDIS interaction were significant (F values across all analyses < 1.77; p values >0.15; see appendix 2 for exact F and p values) p>0.5).

5.0 Discussion

The current study sought to investigate the effects of N₂O gas inhalation (relative to medical air) on declarative recall of ‘traumatic’ events, the relationship between HRV and memory, and potential linguistic markers of trauma. In particular, it addressed two primary research questions: (i) does N₂O inhalation cause global impairment (across voluntary and involuntary memory)? (ii) Due to its dissociative effects, does N₂O decrease narrative cohesion and self-focus in terms of the content of retrieved memories? An additional, exploratory question related to whether there was an association between low levels of HRV (sympathetic dominance) at encoding and subsequent recall and whether this association was dependent on group (N₂O and medical air). Other than Das et al (2016), which focused on involuntary memory, this is the only study describing the effects of N₂O on emotional memory, which may have implications for the treatment and prevention of PTSD. Results of the study did not find significant group differences between the N₂O group and placebo group on emotional memory. Specifically, the study found that N₂O did not decrease narrative cohesion and self focus. We also concluded that N₂O did not alter declarative, voluntary recall of ‘traumatic’ events. The study found that baseline HRV was

correlated with voluntary memory performance, but not involuntary memory. Voluntary recall of the traumatic memory is the main technique of exposure-based psychotherapy for PTSD. Accordingly, further research is needed to continue investigating ways of detecting emotional arousal (e.g. fear and perceived threat) and different states of consciousness such as depersonalisation, derealisation, and flashbacks during voluntary recall of trauma among individuals with PTSD.

5.1 PTSD, emotional memory and N₂O

Dual representation theory of PTSD (Brewin, Dalgleish & Joseph, 1996; 2003; 2014) proposes that during trauma, the encoding of contextualised episodic memories is weakened, whereas the encoding of perceptual memories is strengthened. Therefore, individuals are able to deliberately retrieve contextualised representations, but reminders of the trauma also lead to automatic retrieval of perceptual representations, with a sense of reliving the event (Brewin, 2014; Booker et al., 2018). The current study therefore expected to find that trauma memories would contain greater sensory recall than perceptual recall. This was found to be the case across groups. A further aim of the study (in relation to voluntary memory), was to develop a memory scoring frame for voluntary free recall trauma video data obtained in Das et al (2016), and then to examine the effects of drug on two 'levels' of declarative emotional memory, namely 'gist' and 'detail'. Developing such a scoring frame provides a valuable translational tool for researchers examining memory effects of drugs and experimental behavioural interventions on *voluntary* recall using the specific trauma video described in Das et al (2016), which has also been used in a number of other recent

studies examining pharmacological modulation of emotional memory (Kamboj et al., 2019, Rombold-Bruehl et al., 2018).

NMDA receptor antagonists such as ketamine and N₂O (Kurdi et al., 2014; Nagele et al., 2015; Das et al., 2016) have only recently been explored in relation to psychiatric disorders due to blocking the effects of excitatory glutamate signalling in the central nervous system. Like ketamine, N₂O is a dissociative anaesthetic and primarily an antagonist at the NMDAR (Jevtović-Todorović et al., 1998). The pharmacopoeia of NMDAR-ergic agents is currently very small, its use limited (at least in the case of ketamine) by the potential for acute psychotomimetic and dysphoric effects, and the need for careful monitoring of such effects (Walsh, Das & Kamboj., 2017). Relative to cued recall, examining free recall data had the advantage of allowing a wider examination of drug effects on memory phenomena relevant to trauma, including memory errors (specifically, 'false memory'). Given the association between dissociation and false memory, and based on the dissociative properties of N₂O, it was predicted that those who inhaled N₂O would experience more false memories relative to placebo, and that this effect would be moderated by N₂O-induced dissociation. However, no group differences were observed on memory performance. This suggests that that the level of N₂O administered did not produce adverse effects on voluntary memory, such as memory errors or amnesia. It is possible that changing the dose of gas administered could improve the recall of traumatic memories (gist and/or detail), or due to its dissociative effects decrease narrative cohesion and self-focus.

5.2 Linguistic markers of trauma

The current study also examined the *linguistic content* of memory during free recall using LIWC. Cognitive impairment in trauma narratives are often characterised as both a fragmentation and disorganization in the trauma memory record (Foa et al., 1995). This includes repetitions, disjointed thinking, unfinished thoughts and speech fillers (Brewin, 2016). Recollections of traumas tend to be accompanied by negative emotions and sensory and/or perceptual information (Booker et al., 2018). For example, emotional and sensory utterances have been shown to coincide with poorer outcomes, including more severe depression and posttraumatic symptoms (Eid et al., 2005; Hellowell & Brewin, 2004). Similarly, an affect-laden narrative is consistent with the cognitive model of PTSD (Ehlers & Clark, 2000), such that individuals who have not processed their trauma are more likely to use affect words, typically negative emotion words (Eid et al., 2005; Crespo et al., 2016). The current study aimed to examine whether group differences were evident in the free recall of trauma narratives and whether linguistic markers were related to gist and detail memory. Specifically, following the results of the systematic review in chapter 1, narratives were examined in relation to negative affect, insight, cause, analytic, authentic, and use of pronoun. However, no significant differences were observed suggesting that the properties of N₂O do not significantly affect the quality of trauma narrative with regard to structure and content.

5.3 Heart rate variability as an index of response to trauma memory

Psychological and physiological states in response to trauma reminders or cued recollection of trauma (e.g. script-driven imagery) have been widely studied (e.g. Hopper et al., 2007; Pitman et al., 1987). In studies of PTSD, HRV has been used as an objective measure of reactions to trauma-related stimuli (Chou et al., 2014). Most studies have shown a positive association between PTSD severity and RMSSD increase when trauma memories were involuntarily triggered by reminders (e.g., Adenauer et al., 2010; Ehlers et al., 2010; Hetzel-Riggin, 2010). Flexibility of the autonomic nervous system, indicated by alterations in both the sympathetic nervous systems (SNS) and parasympathetic nervous system (PNS) in response to stress has been associated with better psychological adjustment (Appelhans & Luecken, 2006; Berntson et al., 2008; Thayer et al., 2012). While heightened SNS activation has been suggested to underlie the fight or flight response (Thayer & Lane, 2009), elevated PNS activation has been associated with increased concentration or a state freezing response under extreme stress (Bradley & Lang, 2007; Chou et al., 2014; Hansen, Johnsen, & Thayer, 2003).

Among studies assessing HRV during voluntary recall of trauma, when reliving was not specifically required, significant changes in HRV (relative to a resting baseline) were not found (Cohen et al., 2000, 1998). In contrast, when vivid recall of details was asked for, a significant decrease in HF-HRV was reported, and the reduction was greater among individuals with PTSD than healthy controls (Keary et al., 2009). These studies tentatively suggest an association between varying levels of HRV reactivity and different level of emotional arousal and states of consciousness during voluntary

recall of trauma (Chou et al., 2018). The current study differed from some of the studies above in that HRV was assessed during encoding. therefore hypothesised that (baseline and/or peri-‘traumatic’) HRV would predict intrusive memories, and (by virtue of increased rehearsal of these intrusive memories), also predict voluntary memory at one week follow up. As a preliminary step in determining the role of such predictors in determining potential therapeutic-preventative response of drugs that might be employed in secondary prevention of PTSD, we additionally sought to determine whether drug group moderated any effect of HRV (RMSSD) on subsequent (involuntary and voluntary) memory. However, whilst we found a main effect of HRV and time, we did not find a main effect of group and no group x time interaction. Similarly, although baseline RMSSD was correlated with voluntary memory performance, there were no significant correlations found between baseline RMSSD and involuntary memory (gist and/or detail).

Few studies (e.g. Cohen et al., 2000, 1998; Halligan, Michael, Wilhelm, Clark, & Ehlers, 2006; Keary, Hughes, & Palmieri, 2009) have examined cardiovascular responses during encoding and voluntary recall of traumatic memories (i.e. recall without the presentation of reminders). A lower HR reactivity to the recollection of traumatic memories among individuals with PTSD, compared to that of healthy controls or other clinical populations, has been found in most of these studies (Chou et al., 2018; Cohen et al., 2000, 1998; Halligan et al., 2006). Heightened activation of the SNS has been commonly found as a reaction to involuntarily encountering reminders of traumatic events among individuals with PTSD (e.g. Ehlers et al., 2010; Hetzel-Riggin, 2010). However, very little research has examined how the SNS and PNS respond to voluntary recall of trauma (Chou et al., 2018), which is of great

clinical interest since it is a central procedure in exposure-based therapies (Chou et al., 2018). Voluntary recall of the traumatic memory is the main technique of exposure-based psychotherapy for PTSD. During voluntary recall, full activation of vivid images and raw emotions, as well as the ability to hold these materials in focal attention and integrate them into a meaningful cognitive structure are key elements in successful therapy (Brewin, Gregory, Lipton, & Burgess, 2010; Foa, Steketee, & Rothbaum, 1989). Accordingly, further research is needed to continue investigating ways of detecting emotional arousal (e.g. fear and perceived threat) and different states of consciousness such as depersonalisation, derealisation, and flashbacks (Lanius, 2015) during voluntary recall of trauma among individuals with PTSD.

Studies have shown that higher levels of resting HRV are associated with better performance on tasks that require inhibition, such as those that assess motor-response control (Kryptos et al., 2011) and those that tap broader executive functions, including working memory (Hansen, Johnsen, & Thayer, 2003) and sustained attention (Johnsen et al., 2003). Hovland et al. (2012) found that performance on executive-function tasks that assess inhibition, attentional shifting, and task switching was correlated with HRV; however, the strongest associations were found for measures of inhibition (Gillie, Vasey & Thayer, 2014). Neuroimaging research regarding encoding also suggests that HRV may be associated with brain networks that support memory suppression (Gillie, Vasey & Thayer, 2014). Results from a study by Feeling et al. (2015) suggest that individual differences in resting HF-HRV predict false alarm rates in a memory retrieval situation. Specifically, higher resting HF-HRV predicted lower false alarm rates (lower chance of incorrectly identifying lure memories). The authors claimed that in tasks where individuals were required to

distinguish between true and false memories (e.g. in eyewitness testimony) resting HF-HRV appeared to serve as a proxy of such memory abilities. Since both memory retrieval and encoding are thought to be reflected in this task, HF-HRV may predict both encoding and retrieval abilities. However, research investigating HRV and the encoding of memory is very limited and further studies are needed to support this claim.

5.4 Limitations

To model the processes underlying the encoding of trauma memories and better control for variability, the trauma film paradigm (reviewed by Holmes & Bourne, 2008) has been widely adopted with healthy volunteers (Chou et al., 2014). A previous study (Holmes et al., 2004) adopting this paradigm has found decreases in HR during film viewing, with a greater reduction associated with an increased number of subsequent intrusive images of the film. Moreover, it has been well established that the nature, amplifiers, and attenuators of intrusive memories for the trauma film are in line with those of intrusions that resulted from real traumas (see review by Holmes & Bourne, 2008). Other advantages of the trauma film paradigm include enabling the investigation of peritraumatic phenomena and offer laboratory control (Chou et al., 2014; Holmes & Bourne, 2008). Nevertheless, future studies involving survivors of real-life traumatic events are needed before generalization of the findings can be made with greater confidence.

In addition, data that could have been of potential value, such as a recovery period post-trauma without gas inhalation, was lacking in the current study. This data could

have provided a more nuanced understanding of both encoding and recall of trauma memory. Similarly, the sample size of the study was relatively small (N=49) especially after being separated into the two groups. This is likely to have resulted in the study being underpowered. Replication with bigger sample sizes is therefore needed.

Further research with N₂O is required to replicate these effects in a clinical sample and establish the potential benefits and dangers of its use following traumatic events. As N₂O is an effective and portable analgesic, it is already very widely used by emergency services for pre-hospital pain management (Fisher et al. 2006). It is possible that this practise has unintended (beneficial or deleterious) effects on maladaptive memory formation in the post trauma period. Prospective studies of the development of maladaptive memory following traumatic events where N₂O (or indeed other NMDAergic analgesics, such as ketamine) has been administered as a first-line analgesic will be useful in determining the extent of such effects.

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Part 3. Critical appraisal

1.0 Introduction

This critical appraisal outlines some of the reflections I have developed over the past three years when undertaking this thesis. In particular, it includes experiences of undertaking a systematic review into potential linguistic markers of trauma, working within the field of psychopharmacology for the first time, choosing a project using data previously collected and using new methods to analyse data (LIWC and Kubios).

2.0 Systematic review

I had decided relatively early in the process of choosing a topic for the review that despite having a range of potential review questions (e.g. regarding heart rate variability and trauma recall or NMDA receptor antagonists and mental health outcomes), I wanted the topic to focus on linguistic markers of trauma. In part this was because I thought there would be a greater body of literature to draw from in order to undertake a comprehensive review. However, prior to completing the current thesis I had been interested in investigating trauma narratives beyond the field of the cognitive behavioural model and I was keen to explore this further. When conducting the review I was surprised that despite having a relatively inclusive searching strategy which generated a total of 1839 articles (without duplicates), only 16 studies ultimately met the review's criteria. Further, despite a number of tentative conclusions that were drawn from the review, the 16 articles included a range of samples (clinical versus non clinical) and range of trauma severity. It caused me to reflect more generally on how terms such as 'body of evidence' are used in the scientific community which potentially reflect a relatively small number of studies.

3.0 Experience of psychopharmacological literature

I chose to investigate the empirical study outlined in chapter 2 primarily because of my interest in the relationship between emotional memory and PTSD. The field of psychopharmacology was new to me, as was the literature on physiological changes (heart rate variability) during trauma recall. Whilst I was excited at the prospect of investigating a novel area of research, the first to describe the effects of N₂O on declarative and psychophysiological aspects of emotional memory, it took a long time for me to feel comfortable using the terminology and adapt to the stylistic differences in the literature of this area. For example, I found that relative to studies investigating a psychological therapies approach, which I had been more familiar with, generally sentences were shorter, use of jargon was higher and explanations underpinning the agents of change were more restrictive. Similarly, I found that results sections of papers were generally much larger than the more exploratory discussion and introductory sections. This made learning about the relevant pharmacology literature more challenging particularly in the early stages of writing the thesis.

4.0 Working with secondary data in a novel area of research

I found that working with pre-existing data presented me with both a number of opportunities and advantages as well as potential challenges. In particular, the data allowed for exploratory analysis of a range of variables which had not been previously examined. This meant that the nature of the study could have taken a range of directions allowing for an exciting, novel investigation into the relationship between

emotional memory and trauma. However, this meant that there needed to be a strong rationale supporting hypotheses and investigations. The lack of previous literature specific to memory encoding and nitrous oxide meant that a lot of background research was needed to form a comprehensive understanding of the area around this topic in order to have a solid rationale as to the purpose and foundation of the research I would be conducting.

Developing a scoring frame to make sense of the free recall narratives formed a very time consuming task of the research. For example, considering the format that the coding would take (gist and detail) and ensuring that this was consistent with evidenced based research for the trauma film paradigm. This required planning and a lot of additional research. Second to this time consuming aspect was the coding of the actual trauma videos; a moment by moment detailing of the descriptions of scenes. The frame was then compared to all 49 participant narratives which were coded in a binary “present” or “absent” format (gist, detail, false gist, false detail).

5.0 Using new methods to analyse data

Learning to use new data analysis methods such as LIWC and Kubios was an aspect of the project I was really excited to learn about. I had never used either programmes and feel grateful to have had the opportunity to learn new skills with such complex data. This was particularly true of Kubios which analysed various aspects of heart rate data. I now feel confident in using these programmes having immersed myself in such a new area of research too me and feel proud of my ability to adapt to using unfamiliar methods of data analysis.

6.0 Summary

This thesis provides a novel investigation into declarative recall of trauma memory. I have learned a huge amount through undertaking this research, including both a range of new research skills (such as developing a scoring frame, using LIWC, Kubios and SPSS) and contributing to the knowledge base of psychopharmacological and psychophysiological correlates of trauma. It is hoped that further research into the use of nitrous oxide can be used to replicate these effects in a clinical sample and establish the potential benefits and dangers of its use following traumatic events.

Appendix 1

Appendix 1: NICE (2012) Methodology checklist: randomised controlled trials

Study identification Include author, title, reference, year of publication					
Guideline topic:		Review question no:			
Checklist completed by:					
		Circle or highlight one option for each question			
A. Selection bias (systematic differences between the comparison groups)					
<u>A1</u>	An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	No	Unclear	N/A
<u>A2</u>	There was adequate concealment of allocation (such that investigators,	Yes	No	Unclear	N/A

	clinicians and participants cannot influence enrolment or treatment allocation)				
<u>A3</u>	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect: <ul style="list-style-type: none"> · · · · · 					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
<u>B1</u>	The comparison groups received the same care apart from the	Yes	No	Unclear	N/A

	intervention(s) studied				
<u>B2</u>	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
<u>B3</u>	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
<p>Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?</p> <p>·</p> <p>·</p> <p>·</p> <p>·</p>					
Low risk of bias		Unclear/unknown risk		High risk of bias	
<p>Likely direction of effect:</p> <p>·</p> <p>·</p> <p>·</p> <p>·</p>					
<p>C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)</p>					

<u>C1</u>	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
<u>C2</u>	a. How many participants did not complete treatment in each group?				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
<u>C3</u>	D. For how many participants in each group were no outcome data available? .				
	b. The groups were comparable with	Yes	No	Unclear	N/A

	<p>respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).</p>				
<p>Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?</p> <ul style="list-style-type: none"> · · · · 					
<p>Low risk of bias</p>	<p>Unclear/unknown risk</p>	<p>High risk of bias</p>			
<p>Likely direction of effect:</p> <ul style="list-style-type: none"> · · · · 					
<p>D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)</p>					

<u>D1</u>	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
<u>D2</u>	The study used a precise definition of outcome	Yes	No	Unclear	N/A
<u>D3</u>	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
<u>D4</u>	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
<u>D5</u>	Investigators were kept 'blind' to other important confounding and	Yes	No	Unclear	N/A

	prognostic factors				
<p>Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?</p> <ul style="list-style-type: none"> · · · · 					
Low risk of bias		Unclear/unknown risk	High risk of bias		
<p>Likely direction of effect:</p> <ul style="list-style-type: none"> · · · · 					

Appendix 2

Appendix 2: NICE (2012) Methodology checklist: cohort studies

Study identification					
Include author, title, reference, year of publication					
Guideline topic:			Review question no:		
Checklist completed by:					
			Circle or highlight one option for each question:		
A. Selection bias (systematic differences between the comparison groups)					
<u>A1</u>	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
<u>A2</u>	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
<u>A3</u>	The groups were comparable at baseline, including all	Yes	No	Unclear	N/A

	major confounding and prognostic factors				
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
<u>B1</u>	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
<u>B2</u>	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
<u>B3</u>	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					

Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
<u>C1</u>	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
<u>C2</u>	a. How many participants did not complete treatment in each group?				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
<u>C3</u>	a. For how many participants in each group were no outcome data available?				

	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
<u>D1</u>	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
<u>D2</u>	The study used a precise definition of outcome	Yes	No	Unclear	N/A
<u>D3</u>	A valid and reliable method was used to	Yes	No	Unclear	N/A

	determine the outcome				
<u>D4</u>	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
<u>D5</u>	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias		Unclear/unknown risk		High risk of bias	
Likely direction of effect:					
<ul style="list-style-type: none"> · · · · 					

Appendix 3

Appendix 3: NICE (2012) Methodology checklist: case-control studies

Study identification Include author, title, reference, year of publication			
Guideline topic:		Review question no:	
Checklist completed by:			
Section 1: Internal validity			
		<i>Circle or highlight one option for each question</i>	
<u>1.1</u>	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
<i>Selection of participants</i>			
<u>1.2</u>	The cases and controls are taken from comparable populations	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
<u>1.3</u>	The same exclusion criteria are used for both cases and controls	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
<u>1.4</u>	What was the participation rate for each group (cases and controls)?	Cases: Controls:	

<u>1.5</u>	Participants and non-participants are compared to establish their similarities or differences	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
<u>1.6</u>	Cases are clearly defined and differentiated from controls	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
<u>1.7</u>	It is clearly established that controls are not cases	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
<i>Assessment</i>			
<u>1.8</u>	Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
<u>1.9</u>	Exposure status is measured in a standard, valid and reliable way	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
<i>Confounding factors</i>			
<u>1.10</u>	The main potential confounders are identified and taken into account in the design and analysis	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
<i>Statistical analysis</i>			

1.11	Have confidence intervals been provided?	
<p>Section 2: Description of the study</p> <p>(This information is required for evidence tables to facilitate cross-study comparisons. Please complete all sections for which information is available.)</p> <p><i>Please print clearly</i></p>		
2.1	How many people participated in the study?	<p><i>List the numbers of cases and controls separately.</i></p> <p>.</p> <p>.</p> <p>.</p> <p>.</p>
2.2	What are the main characteristics of the study population?	<p><i>Include all characteristics used to identify both cases and controls – for example, age, sex, social class, disease status.</i></p> <p>.</p> <p>.</p> <p>.</p> <p>.</p>
2.3	What environmental or prognostic factor is being investigated?	<p>.</p> <p>.</p> <p>.</p> <p>.</p>
2.4	What comparisons are made?	<p><i>Normally only one factor will be compared, but in some cases the extent of exposure may be stratified – for example, non-smokers vs light, moderate or heavy smokers. Note all comparisons here.</i></p> <p>.</p> <p>.</p>

		<ul style="list-style-type: none"> · ·
2.5	For how long are participants followed up?	<p><i>This is the length of time over which participant histories are tracked in the study.</i></p> <ul style="list-style-type: none"> · · · ·
2.6	What outcome measure(s) is/are used?	<p><i>List all outcomes that are used to assess the impact of the chosen environmental or prognostic factor.</i></p> <ul style="list-style-type: none"> · · · · ·
2.7	What size of effect is identified?	<p><i>Effect size should be expressed as an odds ratio. If any other measures are included, note them as well. Include p-values and any confidence intervals that are provided.</i></p> <ul style="list-style-type: none"> · · · ·

2.8	How was the study funded?	<p><i>List all sources of funding quoted in the article, whether government, voluntary sector or industry.</i></p> <p>.</p> <p>.</p> <p>.</p> <p>.</p>
2.9	Does this study help to answer your guideline review question?	<p><i>Summarise the main conclusions of the study and indicate how it relates to the review question.</i></p> <p>.</p> <p>.</p> <p>.</p> <p>.</p>

Appendix 4

Appendix 4. Table 4 – Multiple regression output – Gist memory and linguistic variables

LIWC variable	Overall regression model – Gist memory	Model controlling for RMSSD at baseline and dissociation (on-gas CADDSS score)
Negative affect	F=1.153, p=0.339	F=1.773, p=0.158
Insight	F=.834, p=0.482	F=2.152, p=0.096
Cause	F=.696, p=0.559	F=1.644, p=0.186
Analytic	F=.213, p=0.887	F=1.208, p=0.326
Authentic	F=.582, p=0.630	F=1.330, p=0.279
Pronoun	F=.684, p=0.567	F=1.332, p=0.279