

Delayed-onset post-traumatic stress disorder symptoms in dementia

Clara Martinez-Clavera MBChB, MRCPsych, PGCME, Sarah James MBChB (Hons), BSc (Hons), Eva Bowditch MBBS, MRCPsych, Tarun Kuruvilla FRCPsych

Post-traumatic stress disorder (PTSD) is commonly associated with working-age adults and remains largely unrecognised in the elderly. In this review, Clara Martinez-Clavera *et al* consider three examples of delayed-onset PTSD and its frequent association, or misdiagnosis, as one of the numerous manifestations of the behavioural and psychological symptoms of dementia (BPSD). Finally, recommendations for pharmacological and psychological interventions are suggested.

Dementia sufferers commonly experience non-cognitive symptoms as their disease progresses. These symptoms are often labelled as behavioural and psychological symptoms of dementia (BPSD) and encompass a broad range of symptoms relating to mood changes such as depression and anxiety, psychosis, and inappropriate behaviours like wandering, shouting and agitation. PTSD is a common diagnosis amongst working-age adults but it is infrequently diagnosed in the elderly, particularly those with dementia. Previous case reports have published examples of dementia sufferers experiencing PTSD symptoms long after the original traumatic event. Despite these examples, little is known about the manifestation of traumatic exposure in the older adult population. We consider whether delayed-onset post-traumatic symptoms in the elderly are being misdiagnosed, instead falling under the umbrella of BPSD. In this article, we attempt to expand on previous work by describing three cases of delayed-onset PTSD associated with the development of dementia. We explore potential biological and psychosocial theories to explain the aetiology of these symptoms with reference to the literature. We end by considering the clinical implications for future practice, including suggestions for improved diagnosis and management.

Background

The International Classification of Diseases, 10th Revision (ICD-10) defines PTSD as a condition that follows exposure to a stressful event or situation

(either short or long lasting) of exceptionally threatening or catastrophic nature, which may cause pervasive distress. There is persistent remembering or 'reliving' the stressor by intrusive flashbacks, vivid memories, and recurring dreams or by experiencing distress when exposed to circumstances resembling or associated with the stressor. There is also actual or preferred avoidance of circumstances resembling or associated with the stressor (not present before exposure to the stressor). It may include increased psychological sensitivity and arousal such as: difficulty in falling or staying asleep; irritability; outbursts of anger; difficulty in concentrating; hyper-vigilance, and exaggerated startle response. ICD-10 requires symptoms to have emerged within six months of the stressful event, or the end of a period of stress.¹ However, published cases of World War II veterans in the early stages of dementia describe the onset of PTSD after decades of living without symptoms.²⁻⁴ There have also been published cases related to other traumatic events, such as those of Holocaust and Titanic survivors.⁵ In this article, we are expanding on this work by describing three additional cases of delayed-onset PTSD associated with the manifestation of the development of dementia, and discuss a number of hypotheses to explain this association.

Case 1

A retired male in his 70s, was diagnosed with prodromal Alzheimer's disease at a memory assessment service. He had been experiencing short-term memory and word finding difficulties for two years, repeating himself, misplacing objects around the house and struggling to name objects. His computed tomography (CT) head scan showed moderate atrophy in the left median temporal lobe. The onset of his cognitive symptoms was associated with new-onset intrusive flashbacks of a traumatic event that took place while he worked in the military involving the killing of enemy fighters whilst on active duty. These flashbacks were accompanied by restless nights, anger outbursts, increased distractibility and ongoing fear that he may kill someone. He has been signposted to

an army veterans support group. He has agreed to undergo yearly reviews of his cognitive function as well as assessment for cognitive behavioural therapy (CBT) to manage his current psychiatric symptoms, which have been attributed to a delayed PTSD.

Case 2

A 77-year-old man had initially been diagnosed with mild cognitive impairment before it progressed to Alzheimer's disease at the age of 72 years. Initial pharmacological management consisted of donepezil. Family members noted he was becoming increasingly agitated and as a result memantine was added. Donepezil was continued alongside memantine due to its initial effectiveness and the patient being in the early stages of the disease. He eventually required transfer to a care home at the age of 75 years. The Care Home Support Team were asked to review him after two years at the care home due to agitation and misinterpretation of environmental stimuli. At times, he appeared to be trying to clear people from the lounge as he believed there were bombs being dropped. He was also observed multiple times to cower in the corner, appearing frightened and fearful in noisy environments. There was one incident whereby he hit another resident who had been shouting as he felt 'threatened by the enemy'. He was usually noted to express significant anxiety about being attacked and dying as a result. He was observed to be increasingly wakeful at night and he disliked seeing other residents in distress. In the past, he had been involved in bombing attacks as a fighter pilot during the Falklands War. Pharmacological management of his PTSD symptoms included risperidone, which had little effect. Mirtazapine at night was tried with good effect on the patient's behaviour. Non-pharmacological management included the avoidance of noisy environments, additional one-to-one support with carers, reassurance at times of distress and reminiscence therapy.

Case 3

A 90-year-old with Alzheimer's disease was able to manage at home with support during the early to moderate stages of her dementia. She moved into a care home in the later stages of her disease. The staff observed that she became particularly anxious when assisted with activities of daily living and during group activities when she opted to spend time in her room. She disliked physical touch, startled easily and would frequently shout incoherently. At night her sleep was disturbed as she believed soldiers were

attempting to break into the home. As her dementia progressed, she began to communicate more in her native German. She was Jewish and had lived in Europe, witnessing the Jewish community being attacked, rounded up and arrested as anti-Semitism grew before the beginning of World War II. She migrated to the UK before the war began and worked as a teacher. Her family described her as being closed off about the past and reluctant to speak about her traumatic experiences before developing dementia. The care home found that reminiscence work made her symptoms worse though when they focused more on her work as a teacher and positive aspects of her earlier life they noticed an improvement in her well-being. Overall, psychological strategies worked best.

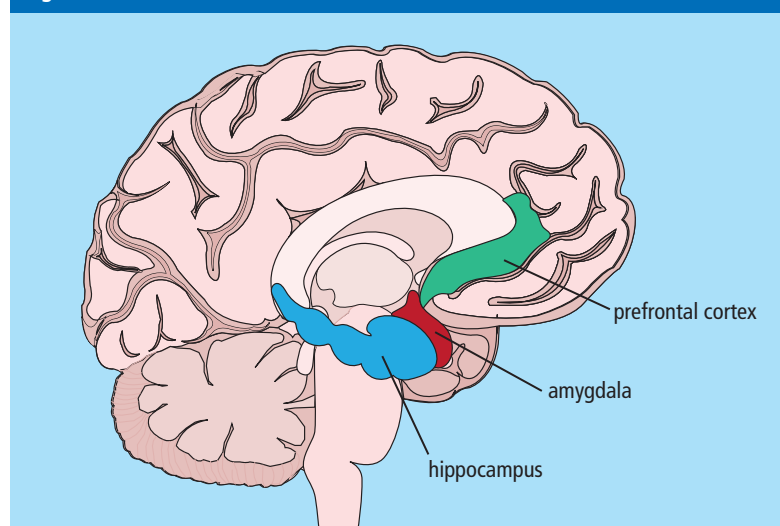
Discussion

Biological theories

Recent research findings highlight a close pathological relationship between PTSD and dementia. For instance, studies using standard neuropsychological instruments have demonstrated memory deficits in patients with PTSD. Moreover, memantine has been shown to improve cognitive, PTSD and mood symptoms in a small open-label trial of 26 veterans with PTSD.⁶ Another study suggests that PTSD patients and trauma-exposed individuals, even without exposure to an evocative stimulus, develop chronic dysfunction of the hippocampus as well as the amygdala.⁷ In the largest ever neuroimaging study of PTSD, a smaller hippocampus and amygdala in PTSD patients has been demonstrated.⁸ In addition to this, a magnetic resonance imaging (MRI) study of 24 soldiers with PTSD and 23 control soldiers showed reduced cortical thickness, primarily in the frontal and temporal lobes, as well as decreased volumes in the right hippocampus and caudate of PTSD soldiers.⁹ Though interestingly, a meta-analysis appears to suggest that, as well as decreased volume in the hippocampi bilaterally, it is a reduction in volume of the left hippocampus that correlates with PTSD symptom severity.¹⁰ Finally, an MRI study of 51 Iraqi Freedom veterans with PTSD symptoms showed that reduced hippocampal volume in trauma-exposed veterans was associated with elevated perceived threat relative to actual combat exposure with an increase in PTSD symptoms, suggesting that the hippocampus is critically involved in the retrospective recall of the subjective impact of traumatic experiences.¹¹

The hippocampus appears to have a role in 'pattern separation', the process by which memories are stored as unique representations that are resistant to

Figure 1. Anatomical structures affected in PTSD



confusion.¹² 'Contextual fear conditioning', a robust form of learning in which an association is made between a specific context representation and its aversive consequences, is thought to underlie PTSD symptomatology, and it has been attributed to the hippocampus (more specifically the dorsal hippocampus) as well as the amygdala.¹³ The circuitry involves, in addition, cortical structures such as pre- and infralimbic ventromedial prefrontal cortex (see Figure 1).¹⁴

'Fear extinction' is a form of learning thought to underlie the suppression of fear memories.¹⁵ Emerging evidence suggests that stress impairs recovery from trauma by impairing fear extinction, with various functional as well as structural abnormalities identified in the hippocampus, prefrontal cortex and amygdala.¹⁵ Such functional abnormalities may underlie the cognitive and emotional disturbances seen in PTSD. In the context of patients who recall traumatic experiences after a long period of time, it is worth noting that remote fear memory returns to a hippocampus-dependent state after long-time recall, as recent research findings appear to suggest. This potentially opens the possibility of targeting the reconsolidation of remote fear memories in the hippocampus in order to facilitate fear extinction in late-onset PTSD.¹⁶

Rodent studies have also shown that stress results in expression of key cholinergic genes in both cortical regions and the hippocampus with enhanced muscarinic receptor-mediated glutamatergic transmission, which is thought to underlie the hippocampal dysfunction that seems to occur after stress.¹⁷ This may explain the therapeutic benefits of the anti-glutamatergic agent memantine that has been

observed in veterans with PTSD. Other studies also highlight the transient increase in the levels of acetylcholine and a phase of enhanced neuronal excitability following a period of stress,¹⁸ possibly explaining the apparent exacerbation of PTSD symptoms in dementia patients who are taking acetylcholinesterase inhibitors.¹⁹

Finally, with passage of time following trauma, PTSD patients also appear to show an increased fear response to a wide range of neutral cues, a phenomenon known as 'fear generalisation'.²⁰ This time-dependent fear generalisation appears to result from loss of precision of memories over time, or perhaps loss of the 'pattern separation', which is thought to result from degradation of underlying cortical representations. Other studies seem to suggest that such degradation involves reduced inhibition in the hippocampus and frontal areas, which would appear consistent with the previously mentioned glutamatergic excitability, and this could therefore explain the emergence of PTSD symptoms over time.²¹ It is also worth considering sensory impairment and environmental changes, such as moving to a care home, as additional contributing factors for the misinterpretation of neutral cues.

Psychosocial theories

In a previous article on the emergence of PTSD in trauma survivors with dementia, the authors hypothesised that a dementing process may be interfering with ego defence mechanisms that had previously been effective at warding off traumatic memories.⁵ In patients with PTSD, an unconscious driven process involving the repeated experiencing of trauma, termed 'repetition-compulsions', has been considered as a mechanism used to resolve unwanted emotions associated with the original traumatic experience. Immature defence mechanisms such as splitting and projection have been identified as ways in which the unconscious tries to block awareness of the trauma.²² For some people with dementia it appears that their ability to utilise these processes are compromised, as observed by the increase in intrusive symptoms such as flashbacks and nightmares. With the loss of ability to effectively use defence mechanisms, re-experiencing mechanisms may be activated. Could this be related in part to changes in cognition and reduced appreciation of reality disturbing the normal processes of the ego?

Reconciliation also brings us to the idea that, as people age, they are more likely to focus on their past and enter Erikson's eighth stage of psychosocial

ing age, may also affect the ability to escape this negative thinking cycle by means of applying healthy strategies, *eg* 'behavioural activation'.

Finally, we should consider the possibility that these patients may have suffered from low-grade symptoms of PTSD prior to the development of dementia, which went unidentified or undisclosed. Late-onset stress symptomatology (LOSS) is the term that has been used for such subthreshold PTSD that has been observed in elderly people with previous combat exposure. It is characterised by the development of increasing thoughts and reminiscences about, and emotional responses to, their wartime experiences.²⁶⁻⁸ We hypothesise that the lack of identification or disclosure of symptoms of LOSS or PTSD may have also been due

ing age, may also affect the ability to escape this negative thinking cycle by means of applying healthy strategies, *eg* 'behavioural activation'.

Finally, we should consider the possibility that these patients may have suffered from low-grade symptoms of PTSD prior to the development of dementia, which went unidentified or undisclosed. Late-onset stress symptomatology (LOSS) is the term that has been used for such subthreshold PTSD that has been observed in elderly people with previous combat exposure. It is characterised by the development of increasing thoughts and reminiscences about, and emotional responses to, their wartime experiences.²⁶⁻⁸ We hypothesise that the lack of identification or disclosure of symptoms of LOSS or PTSD may have also been due

to the lack of personal and societal understanding of the condition at the time of the trauma, or fear of reporting symptoms due to stigma.

Clinical implications

It is well recognised that early-onset PTSD is closely related to the development of dementia in later life. The structural changes seen within the brain following traumatic exposure, such as hippocampal atrophy, may contribute to the decline in cognition often seen in patients with PTSD. In patients with a history of trauma but no diagnosis of PTSD, these structural changes may support a diagnosis of dementia but may also indicate those at potential risk of delayed-onset PTSD. Significant left hippocampal atrophy may be associated with more severe PTSD symptoms in later life. Consequently, we may be able to use imaging as a method of identifying those patients who may be susceptible to developing delayed-onset PTSD. This would enable initiation of early management.

The identification of delayed-onset PTSD in residential care is challenging. Patients displaying emotional disturbances are often treated in accordance with guidelines for the management of BPSD. However, patients displaying these symptoms may in fact be experiencing symptoms of delayed-onset PTSD. Consequently, it is essential that a detailed trauma history becomes a routine part of the memory assessment to identify those patients who may be at risk. Limitations to collecting this information include time constraints, a lack of awareness of PTSD amongst professionals and a lack of valid assessment tools. Professionals may be less likely to ask for details due to fear of causing upset, embarrassment or offence for those involved. Patients may be reluctant to report trauma unless asked directly and older adults may minimise its importance due to the traumatic event being in the past or due to fear of stigma. It is essential that this information is gathered before significant cognitive decline occurs. If a patient presents with more advanced dementia it may be appropriate for clinicians to gather this information from carers or relatives.

Currently, evidence on the efficacy of treatment for delayed-onset PTSD in patients with dementia is lacking. Psychological therapies may be appropriate for patients in the earlier stages of cognitive decline. Patients with significant trauma identified at initial memory assessment should be referred for psychological therapy if demonstrating suitable cognitive reserve. This may enable patients to revisit healthy coping strategies and may help strengthen defence

Table 1. Processes believed to underlie PTSD symptomatology

Pattern separation	Process by which memories are stored as unique representations that are resistant to confusion
Contextual fear conditioning	A robust form of learning in which an association is made between a specific context representation and its aversive consequences
Fear extinction	A form of learning thought to underlie the suppression of fear memories
Fear generalisation	Increased fear response to a wide range of neutral cues after a long period of time

mechanisms that were unconsciously applied prior to the onset of cognitive impairment. In addition, cognitive stimulation therapy may help slow cognitive decline and improve quality of life.²⁹ Psychotherapy and trauma-focused techniques may cause an increase in autonomic activity and therefore it is essential to assess physical health prior to treatment.³⁰ Furthermore, the presence of cognitive decline may impact on memory, concentration, attention and learning and therefore sessions may need to be modified in order to meet patients' needs. Reminiscence therapy may be of limited benefit to patients in the later stages of dementia but emphasis on positive life events may help to avert thoughts away from past traumas. Environmental modifications may help to minimise misinterpretation of neutral cues. The use of red, amber, green (RAG) charts may provide carers with a stepwise approach to identifying environmental triggers in order to minimise them. Physical symptoms such as pain should be addressed to reduce distress and minimise the association with past traumatic events.

First-line pharmacological management of PTSD symptoms includes the use of selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs), which have been shown to be effective in reducing symptom severity. Clinicians may consider using these in combination with anti-dementia medication. If acetylcholinesterase inhibitors exacerbate PTSD symptoms, we should consider using them with caution in patients who may be susceptible to delayed onset PTSD. Memantine is a suitable alternative, which may provide therapeutic benefit to those experiencing PTSD symptoms. There is little evidence to support the use of antipsychotics

or hypnotics for delayed-onset PTSD in dementia but these may be considered with caution for particularly distressed patients with little or no response to other first-line pharmacological agents.

Conclusion

The incidence of delayed-onset PTSD in patients with dementia may be more widespread than previously recognised. Biological and psychosocial theories offer possible explanations for the aetiology of PTSD in dementia. In order to increase the identification of these patients, a concise trauma history must become a key component of the memory assessment. Recognition of early life trauma will enable patients to access vital psychological therapy in the early stages of dementia prior to significant cognitive decline. In addition, the awareness of significant trauma exposure in earlier life can help clinicians differentiate between BPSD or delayed PTSD in patients suffering with emotional and behavioural disturbances in more advanced dementias. Symptoms can then be addressed using appropriate environmental and pharmacological management.

Dr Martinez-Clavera and Dr Bowditch are Higher Specialist Trainees in Old Age Psychiatry; Dr Kuruvilla is a Consultant in Old Age Psychiatry, all at 2gether NHS Foundation Trust, Cheltenham, and Dr James is a GP Speciality Trainee at Gloucestershire Hospital NHS Trust working at 2gether NHS Foundation Trust.

Declaration of interests

No conflicts of interest were declared.

References

1. World Health Organization (WHO). *International Statistical Classification of Diseases and Related Health Problems 10th Revision* (ICD-10). Geneva: WHO, 1992.
2. Johnson D. A series of cases of dementia presenting with PTSD symptoms in World War II combat veterans. *J Am Geriatr Soc* 2000; 48(1):70–2.
3. Mittal D, Torres R, Abashidze, et al. Worsening of post-traumatic stress disorder symptoms with cognitive decline: case series. *J Geriatr Psychiatry Neurol* 2001;14(1):17–20.
4. Dallam D, Mellman T, Bhatnagar A, et al. Trauma reenactments in aging veterans with dementia. *J Am Geriatr Soc* 2011;59(4):766–8.
5. van Achterberg M, Rohrbach R, Southwick S. Emergence of PTSD in trauma survivors with dementia. *J Clin Psychiatry* 2001;62(3):206–7.
6. Ramaswamy S, Madabushi J, Hunziker J, et al. An open-label trial of memantine for cognitive impairment in patients with posttraumatic stress disorder. *J Aging Res* 2015;2015:934162.
7. Marin MF, Song H, VanElzakker MB, et al. Association of resting metabolism in the fear neural network with extinction recall activations and clinical measures in trauma-exposed individuals. *Am J Psychiatry* 2016;173(9):930–8.

8. Morey R, Logue M, van Rooij S, et al. Smaller amygdala and hippocampal volume in posttraumatic stress disorder from multi-site investigation by ENIGMA and PGC consortia. Abstract in ACNP 55th Annual Meeting: Poster session III. *Neuropsychopharmacology* 2016;41:S455–630.
9. Sussman D, Pang E, Jetly R, et al. Neuroanatomical features in soldiers with post-traumatic stress disorder. *BMC Neurosci* 2016;17:13.
10. Nelson M, Tumpap A. Posttraumatic stress disorder symptom severity is associated with left hippocampal volume reduction: a meta-analytic study. *CNS Spectr* 2016;1–10.
11. Grupe D, Hushek B, Schoen A, et al. Perceived threat bias and hippocampus volume in trauma-exposed veterans. Abstract in Society of Biological Psychiatry 2016 Annual Meeting *Biological Psychiatry* 2016;79(9):S1–137.
12. Lopresto D, Schipper P, Homberg J. Neural circuits and mechanisms involved in fear generalization: implications for the pathophysiology and treatment of posttraumatic stress disorder. *Neurosci Biobehav Rev* 2016;60:31–42.
13. Chang S, Liang K. The hippocampus integrates context and shock into a configural memory in contextual fear conditioning. *Hippocampus* 2017;27:145–55.
14. Izquierdo I, Furini C, Myskiw J. Fear memory. *Physiol Rev* 2016; 96(2):695–750.
15. Maren S, Holmes A. Stress and fear extinction. *Neuropsychopharmacology* 2015;41(1):58–79.
16. Ishiwaka R, Fukushima H, Kida S, et al. Hippocampal neurogenesis enhancers promote forgetting of remote fear memory after hippocampal reactivation by retrieval. *eLife* 2016;5 pii:e17464.
17. Pavlovsky L, Bitan Y, Shalev H, et al. Stress-induced altered cholinergic–glutamatergic interactions in the mouse hippocampus. *Brain Res* 2012;1472:99–106.
18. Kaufer D, Friedman A, Seidman S, et al. Acute stress facilitates long-lasting changes in cholinergic gene expression. *Nature* 1998; 393(6683):373–7.
19. DeFillo D, Drickamer M. Post Traumatic Stress Disorder (PTSD) and Acetylcholinesterase Inhibitors (ACHEI): A potential nightmare! 2012 American Geriatrics Society 2012 annual scientific meeting abstract book. *Journal of the American Geriatrics Society* 2012;60:S1–242.
20. Guo J, Fan, Y, Ai Q, et al. A deep relevance matching model for ad-hoc retrieval. *Proceedings of 25th ACM International Conference on Information and Knowledge Management (CIKM '16)*. ACM, New York, NY, USA, 55–64. doi: <https://doi.org/10.1145/2983323.2983769>
21. Van Rooij S, Stevens J, Ely T, et al. Inhibition-related hippocampal activation one month post-trauma predicts PTSD symptoms at three months. Abstracts of the Society of Biological Psychiatry 2016 annual meeting. *Biological Psychiatry* 2016;79(9).
22. Price J. Cognitive schemas, defence mechanisms and post-traumatic stress symptomatology. *Psychol Psychother* 2007;80(3):343–53.
23. Erickson EH, Erikson JM, Kivnick HQ. *Vital involvement in old age*. 1st ed. London: Norton, 1986.
24. Torges C, Stewart A, Duncan L. Achieving ego integrity: Personality development in late midlife. *J Res Pers* 2008;42(4):1004–19.
25. Buffum MD, Wolfe NS. Posttraumatic stress disorder and the World War II veteran. *Geriatr Nurs* 1995;16(6):264–70.
26. Davison EH, Pless AP, Gugliucci MR, et al. Late-life emergence of early-life trauma: The phenomenon of late-onset stress symptomatology among aging combat veterans. *Res Aging* 2006;28:84–114.
27. King LA, King DW, Vickers K, et al. Assessing late-onset stress symptomatology among aging male combat veterans. *Aging Ment Health* 2007;11:175–91.
28. Potter CM, Kaiser AP, King LA, et al. Distinguishing late-onset stress symptomatology from posttraumatic stress disorder in older combat veterans. *Aging Ment Health* 2013;17(2):173–9.
29. Spector A, Thorgrimsen L, Woods B, et al. Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. *Br J Psychiatry* 2003;183:248–54.
30. US Department of Veterans Affairs. PTSD assessment and treatment in older adults (www.ptsd.va.gov/professional/treatment/older/assessment_tx_older_adults.asp; accessed June 2017).