Randomised controlled trial of 3MDR for Treatment Resistant Post-traumatic Stress Disorder (PTSD) in military veterans
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1: Background

1.1. The majority of those who serve in the UK armed forces do well after they leave. Military service, particularly combat experience can, however, have adverse effects and these are of concern for the armed forces, other government departments, service personnel and veterans, and their families. Successive UK governments have been accused of neglecting veterans, with reports that homelessness, imprisonment, unemployment and alcoholism are the fate of many. It is estimated that 7.4% of British regular military veterans meet the criteria for PTSD and 17% of those who been have deployed in a combat role, compared to 4.4% of the civilian population. The financial and social impact is considerable. Many veterans with PTSD struggle in their transition to civilian and family life, are unable to work and are in receipt of long-term incapacity benefits.

1.2. Only a limited proportion of people in the general population who suffer mental health problems seek professional help. Among military populations this is true of veterans and serving personnel, albeit to a lesser extent. Engaging serving personnel and veterans in mental health treatment programmes can be challenging due to stigma, perceived weakness in acknowledging emotional difficulties, and military macho cultures. That said, a recent report found that the impact of stigma on help-seeking is not significant, and that other barriers are more important, e.g. failure to recognise having a mental health problem, and negative beliefs about/experiences of treatment and provision of support. Most studies have found that informal sources of help such as family, friends and clergy, are preferred.

1.3. In serving military and veteran populations, recent trials of the first-line trauma-focused interventions known as Cognitive Processing Therapy (CPT) and Prolonged Exposure (PE) have shown clinically meaningful improvements for many patients with PTSD. However, non-response rates have been high, many patients have continued to experience symptoms, and trauma-focused interventions only show marginally superior results compared with active control conditions.

1.4. There is limited existing research into treatment-resistant PTSD and even more limited significant advances. Emerging work with MDMA-assisted psychotherapy shows promise but is unlikely to be appropriate for all people with treatment-resistant PTSD. Pharmacological augmentation strategies have had modest success but have not achieved the step-change required. The 2018 International Society for Traumatic Stress Studies (ISTSS) prevention and treatment guidelines and the 2018 update of the NICE guidelines for PTSD provide strongest support for trauma-focused psychological treatments, which have a positive albeit often partial and sometimes absent effect. Smaller, yet still positive, effects were found for a range of other therapeutic options including pharmacological and non-trauma focused psychological treatments. In addition, a number of novel treatments were found to have emerging evidence of effect in individuals who had already tried other treatments (e.g. neurofeedback and transcranial magnetic stimulation (TMS)).
The current evidence points to a clear need for improvement in existing PTSD treatments and for the development and testing of novel treatments, including more intense interventions for those who have not responded to less intense interventions.

1.5. Modular motion-assisted memory desensitisation and reconsolidation (3MDR)\(^{20}\) is a new treatment that aims to reduce cognitive avoidance and augment engagement with therapy. 3MDR is based on known therapeutic principles of virtual reality exposure therapy\(^{21}\) and eye movement desensitisation and reprocessing (EMDR)\(^{22}\), embedded in a novel context in which the patient walks on a treadmill whilst interacting with a series of self-selected images that are displayed on a large screen. Exposure by virtual reality, enhanced with walking, music and high affect pictures, eliminates cognitive avoidance during exposure and promotes presence. This is an important distinction between 3MDR and traditional trauma focused techniques which are sedentary; patients learn how to move through their avoidance by, literally, walking back into their trauma memory.

1.6. In 3MDR, a dual task is used to facilitate desensitisation and reconsolidation of the emotional content of the traumatic event that is captured on a service-related photograph. This is congruent with working memory theory, which has been used to explain the therapeutic mechanism of EMDR\(^{23}\). According to this theory, working memory has limited resources; if a dual task (for example, following a specific object with your eyes) uses some of those resources, less memory will be available for other memory processes, which in turn will make the recollection of memories less vivid and less affect-laden. In 3MDR, the dual task is different from most EMDR treatments. Instead of making eye movements (or alternative bilateral stimulation) alone, numbers need to be called out whilst the patient is also walking, thereby optimally taxing working memory.

1.7. Preliminary results from research conducted by the originators of 3MDR in the Netherlands regarding the efficacy of 3MDR in veterans with treatment resistant, service-related PTSD are promising. A pilot study\(^{20}\) showed a decrease in PTSD symptoms and no dropouts from the treatment, with the two participants positive about the treatment. No adverse effects were reported and we, therefore, decided to explore the potential efficacy of 3MDR further.
2: Aims and objectives

2.1. The main aim of the proposed research was to determine whether 3MDR was able to reduce traumatic stress symptoms in British military veterans with treatment-resistant, service-related PTSD, to a significantly greater degree than being on a waiting list for 3MDR.

2.2. The main objective was to answer the eight research questions in the table below.

Table 1: Research questions

A  For British military veterans with treatment-resistant, service-related PTSD, does 3MDR reduce symptoms of PTSD as measured by the CAPS5 to a significantly greater degree than being on a waiting list for 3MDR?

B  For British military veterans with treatment-resistant, service-related PTSD, what is the impact of 3MDR on quality of life, functioning, symptoms of depression and anxiety, insomnia, alcohol and illicit substance use and perceived social support?

C  Is 3MDR acceptable to British military veterans with treatment-resistant, service-related PTSD and those delivering the intervention as measured by qualitative semi-structured interviews?

D  What is the likely effect size of 3MDR?

E  What factors may impact efficacy and successful roll-out of 3MDR for treatment-resistant, service-related PTSD, if 3MDR is shown to be efficacious? (Mechanism and process evaluation)

F  What is the behavioural response of the 3MDR sessions in terms of stress and cognitive processing during different dual task phases and how can this guide us in optimal design of the intervention and a Phase III definitive randomised controlled trial? (Mechanism evaluation)

G  Can examination of the integrity of the study protocol, trial recruitment rate, self-report outcome measures, clinician administered outcome measures, randomisation procedure, treatment integrity and acceptability enhance decision making in planning a Phase III definitive randomised controlled trial?

H  Is a definitive randomised controlled trial indicated and feasible?
3: Methods

3.1. The study received ethical and NHS research approval and took place in the Schools of Medicine and Healthcare Sciences at Cardiff University Hospital of Wales. Forty-two military veterans living in South Wales who continued to experience service-related PTSD following treatment with trauma-focused psychological therapy took part in the study. Participants completed a baseline assessment and were then randomised (allocated by chance) to receive 3MDR immediately or after a delay of 14 weeks, with follow-up assessments occurring at 12 and 26 weeks post randomisation. Retention rates were very high; 83% (35 participants) at 12 weeks and 86% (36 participants) at 26 weeks.

3.2. The main outcome considered was symptoms of PTSD. Other outcomes measured were quality of life/functional impairment, depression, anxiety, sleep, alcohol use and social support.

3.3. Eleven of the participating veterans and all six of the 3MDR therapists participated in a single qualitative interview, designed to provide greater understanding about 3MDR, the experience of receiving it and of delivering 3MDR, and of being involved in the research trial. Participating veterans were selected in a manner to ensure learning from as wide a range of individuals as possible, with different characteristics and experiences.
4: The 3MDR Therapy

4.1. The 3MDR therapy was delivered weekly over nine weeks by six experienced psychological therapists, including two military veterans, who work with Veterans’ NHS Wales and Cardiff University. The waiting list group received no intervention for 14 weeks and then received 3MDR over nine weeks.

4.2. Video clips that demonstrate 3MDR can be found via the following links:

https://www.youtube.com/watch?v=j0CklR0P1RI
https://www.youtube.com/watch?v=lUnWe7tfgSQ
https://www.youtube.com/watch?v=bOAbDv-Ai6o

4.3. Prior to the 3MDR sessions, participants were asked to select and bring 12 pictures (from their personal records or the Internet) that evoked memories of the traumatic event. The therapists guided the participant to limit avoidance during picture selection. Supported by the therapist, the pictures were arranged according to psychological distress (SUD) score and theme. For each session, a maximum of 7 out of the 12 pictures were used and selected based on the SUD score or a particular theme. Pictures could be repeated during a session, particularly if the associated SUD score was high, reducing the number of pictures used for some sessions. Participants also chose two pieces of music: the first piece was for the mental and physical warm-up walk to take the participant back to the time of their traumatic event (i.e. music that reminded them of this period); the second piece was for the warm-down to bring the participant back to the here and now and remind them that they were now safe. This was likely to be a more recent piece of music.
5: Results

5.1. All participants were male. The main traumatic events suffered were: severe human suffering; serious injury, harm or death you caused to someone; fire or explosion; combat or exposure to a warzone; sudden, violent death (homicide, suicide); sudden unexpected death of someone close to you; physical assault; assault with a weapon; sexual assault (rape/attempted rape); and captivity (kidnapping, abduction etc.). The average age of participants was 42 and the mean time since their worst traumatic event was over 19 years. The vast majority of participants were White British (95%), and around a third were employed and a third unable to work. Almost half the participants also had a depressive disorder.

5.2. PTSD symptom severity was statistically and clinically significantly better for the immediate treatment group (37% average reduction of PTSD symptoms after receipt of 3MDR) than the delayed treatment group (14% average reduction in PTSD symptoms whilst waiting for 3MDR) at the 12-week follow-up point, which shows a 19% greater reduction in PTSD symptoms for the immediate treatment group over the delayed treatment group at that point. The delayed treatment group experienced an average 28% further PTSD symptom reduction following 3MDR and the immediate treatment group maintained their improvement at 26-week follow-up. It is important to note, however, that not all participants improved following 3MDR, and some reported increased symptoms. 3MDR was found to have a moderate treatment effect despite it being tested in veterans with treatment-resistant PTSD.

5.3. 3MDR was found to be acceptable to most, but not all, participants, but acceptable to all the therapists delivering the intervention, albeit with recommendations from both participants and therapists on what could be done to enhance its effect and acceptability. Key findings in this latter regard included the appropriate assessment and selection of potential candidates for 3MDR, enhanced preparation in advance of 3MDR, the number of treatment sessions available, support between sessions and greater flexibility with respect to content of later 3MDR sessions.

5.4. All ten veterans who experienced therapy, including those who declined opportunities to complete the full course of 3MDR on offer, said that they had been helped. One participant said:

“It was interesting, about session three it was like my brain was being rewired, it’s very hard to describe it but there was something happening in my brain and I was feeling, I was feeling better, even though I got a bit upset now but that’s, but something was happening in my brain and I was feeling better. It’s very hard to put my hands on it but the result is I am sleeping, I am not getting half as upset, and my mood is generally good.”
6: Personal story

6.1. Matt Neve was a Senior Aircraftman in the RAF until being discharged in 2004. He was introduced to 3MDR by his Veterans NHS Wales therapist having already tried a number of other trauma-focused therapies. He has agreed to share his personal experiences of taking part in this study. Matt said, “I had done other therapies like EMDR and CBT and they worked to a point. My therapist said, ‘Look, there’s this trial, I think you might be suitable: do you want to give it a go?’ 3MDR sounded ideal: it’s there, it’s in front of your face and you can’t avoid it.”

6.2. Reflecting on having taken part in the trial and having completed a course of 3MDR, Matt went on to say how, “It has helped. It has definitely helped with my daytime symptoms. My nighttime issues are still there, unfortunately, but through 3MDR I’ve opened up. I talk a lot more about it, I’ve been more open and I’ve definitely benefited.” He added that: “3MDR is not a cure. It softens the symptoms but doesn’t get rid of them. A big part is accepting that, and learning how to manage.”

6.3. Matt also said how preparation for 3MDR and ongoing support outside of therapy sessions are important: “You need sessions before on grounding, and it’s important to be in the right frame of mind. Having a good support network is important. I started to struggle, and if it wasn’t for my wife, her parents and my therapist I might have stopped.” Matt is now using his experiences in a new role as public and patient member of the 3MDR research team, and is part of a group seeking additional funding to test 3MDR with non-military populations affected by trauma.
7: Discussion

**Main Results**

7.1. This study provides quantitative and qualitative evidence that 3MDR is able to reduce traumatic stress symptoms in British military veterans with treatment-resistant, service-related PTSD.

7.2. The mean difference in PTSD scale scores between the intervention group and the control group at 12 weeks is likely to be clinically significant and represents a 19% reduction in PTSD compared with the baseline mean scores. It is noteworthy that being on the waitlist also resulted in a 14% reduction on the PTSD scale, suggesting some form of positive impact at the prospect of treatment in individuals with hitherto treatment refractory symptoms. The total reduction pre-post treatment of those receiving 3MDR immediately represented a clearly clinically significant 37% reduction in PTSD symptoms at presentation.

7.3. Participants allocated to the control group (ie delayed treatment) also responded well to 3MDR, and those who were in the initial treatment group maintained their improvement at 26-week follow-up.

7.4. 3MDR also resulted in statistically significantly greater improvements in self-reported anxiety and insomnia. There was, however, no significant difference between the groups on functioning, depression, health-related quality of life, alcohol misuse and perceived social support.

7.5. The apparent positive impact of 3MDR on the secondary outcome measures of anxiety and insomnia is consistent with studies of other successful treatments for PTSD, suggesting generalisation of positive effects to other groups of symptoms. The absence of effect on alcohol use is perhaps not surprising as those included did not report significant substance misuse problems at baseline. The lack of improvement for functioning, depression, health-related quality of life and increased perceived social support is somewhat disappointing as improvements in these measures are often reported following effective treatment for PTSD.

7.6. 3MDR was found to be acceptable to most, but not all, participants and to all the therapists delivering the intervention, albeit with recommendations from both participants and therapists on what could be done to enhance its effect and to support people during treatment. The study results highlight the fact that 3MDR is not acceptable to all British military veterans with treatment-resistant, service-related PTSD. This is an important finding and further work is underway with data generated from the study to determine those factors associated with better and worse treatment outcomes. These analyses will help with the refinement of selection criteria for 3MDR to ensure that individuals who are unlikely to benefit, or more likely to be adversely affected by it, are not offered 3MDR in future research/clinical practice.

7.7. Rich learning was achieved with respect to the factors that may impact efficacy and successful roll-out of 3MDR for treatment-resistant, operationally-related PTSD. Key findings in this regard
7: Discussion continued...

included the appropriate assessment and selection of potential candidates for 3MDR, enhanced preparation in advance of 3MDR, the number of treatment sessions available, support between sessions, and greater flexibility with respect to content of later sessions.

7.8. Key insights to the active ingredients of the 3MDR treatment package were obtained from the qualitative interviews with participants and therapists. A number of participants and therapists felt that more sessions either on the platform or to help integrate/facilitate the platform work would have been beneficial. Several therapists felt that some trauma-focused psychological treatment after the platform session would have resulted in greater improvement for some participants. These findings will be used to refine the 3MDR treatment protocol and optimally design the intervention for further evaluation. It is likely that an increased maximum number of sessions will be allowed, with a suggested minimum number of platform sessions and then some flexibility regarding the content of further treatment sessions.

7.9. The study protocol worked well for the study overall. It was clear that many of the approaches adopted by the protocol for this study were entirely fit for purpose and would be appropriate to use in a larger RCT. The approach to identifying and approaching potential participants worked well and take-up by those approached was very high. Involvement of a clinician and regular contact/support provision between sessions proved important; indeed it was felt that support between sessions should be enhanced and formalised more in the future and that it should be available to all participants in future studies. Regular contact/support between sessions also helped with retention of participants, which was high.

7.10. The results of the study strongly suggest that a definitive RCT of 3MDR is indicated and feasible.

Results in the context of other research

7.11. Results from the only other early phase randomised controlled trial of 3MDR, conducted by the originators of 3MDR in the Netherlands, followed a somewhat different protocol in that “usual care” was allowed for a certain number of sessions and follow-up was at the end of treatment (whenever that was) rather than a specific time post-randomisation. Both these factors would be expected to improve outcomes, yet the mean PTSD reduction was lower than in this study at the end of 3MDR platform sessions.

7.12. The Wales and Netherlands trials taken together point to the potential effectiveness of 3MDR and its position as a major candidate for further evaluation. There is an urgent need to identify effective treatments for people with PTSD who do not respond to, or are unable to engage with, current first line treatments. If further work confirmed the results of this study, 3MDR would offer a new treatment option with the potential to treat hitherto untreated PTSD and reduce the burden of this debilitating condition to individuals, those around them and to society overall. This would result in an additional option of treatment for people with PTSD at a point when, currently, effective
active treatment possibilities are often exhausted and the prospects of further recovery low.

7.13. The results of the two RCTs of 3MDR mean that 3MDR would have met the criteria for a recommendation of a treatment with emerging evidence, if the results of the two RCTs had been finalized and available in time to inform the recommendations by the ISTSS Guidelines Committee. The results will be able to inform the ISTSS Guidelines Committee when the recommendations are next updated. The effect sizes found places 3MDR on a level with neurofeedback and transcranial magnetic stimulation, as more complicated treatments with emerging evidence of effect in people with likely more treatment-resistant forms of PTSD.

7.14. It is difficult to draw any mechanistic conclusions from the data analysed to date. 3MDR is clearly a complex intervention and it is not known exactly how it works. The results appear to support the combination of elements involved in 3MDR and, in the absence of dismantling studies, Van Gelderen et al’s\textsuperscript{25} model for 3MDR. The model proposes that virtual reality increases presence and attention during treatment to facilitate memory retrieval with the pictures and music personalising the experience. They note the positive effect of physical activity on fear extinction, associative thinking and cognitive theory, providing a rationale for decreased avoidance by walking towards cues of the traumatic memories. The bilateral stimulation requiring dual-attention further facilitates new learning and reconsolidation. They also argue that novel elements of the intervention, absent from many standard PTSD treatments, include activation, personalisation and empowerment.

**Strengths and limitations**

7.15. This was a well-designed RCT that adhered to current methodological recommendations for this type of work. The study was designed as a feasibility trial and, therefore, the number of participants was restricted to 42. A larger sample size would be required for a definitive trial and it is important that the limitations in terms of absolute power are acknowledged when considering the results of this study.

7.16. A major strength of the study was the careful training and supervision of the therapists, along with fidelity checks demonstrating good adherence to the 3MDR treatment protocol. That said, a number of the therapists reported gaining confidence as they treated more participants and it may be that earlier participants may have responded better (i.e. in terms of greater symptom reduction) if treated when the therapists had more confidence and experience with the technique.

7.17. Another key strength of the study was the utilisation of both quantitative and qualitative approaches, thereby allowing results to be cross-referenced from different sources to corroborate or challenge outcomes. The quantitative and qualitative results were very consistent which strengthens the belief that the results are likely to provide a true reflection of the efficacy of 3MDR.

7.18. The significant improvement in members of the delayed treatment group before they received
3MDR does make interpretation more difficult than if there had been no response. It is always difficult to identify a perfect control condition; it may be that had the control condition have been ‘to receive no treatment at all’ (i.e. as opposed to receiving delayed treatment where the anticipation and hope of 3MDR being effective was enough to start reducing the PTSD symptoms among waiting participants), that this ‘no treatment’ control would have provided a better estimate of the absence of treatment by removing the anticipation/hope effect. This was, however, not felt to be ethically optimal for this study and the cross-over design also provided additional information that has been helpful, not least the further improvement post 3MDR in the delayed treatment group.

**Clinical Implications**

7.19. Due to the preliminary nature of this work, it would be premature to recommend 3MDR for routine clinical practice. If 3MDR were to be shown to be effective for treatment-resistant PTSD, it would likely have great appeal to commissioners and practitioners as it would fill a current gap in service provision. The impact on clinical practice and services would be marked, as the potential magnitude of health gain (suggested by early phase studies) through providing this emerging new treatment is substantial. If these effects were to be replicated and then successfully implemented in the NHS and beyond, thousands more people with PTSD could recover, with the availability of 3MDR heralding a new era in the evidence-based care options available to people with PTSD.

**Research Implications**

7.20. As would be expected at this stage of 3MDR’s development, the research implications are far greater than the clinical implications, the main one being that the results indicate the desirability of a pragmatic effectiveness RCT of 3MDR.

7.21. This feasibility study only included military veterans with PTSD secondary to operational experience. There is no reason to believe that non-military veterans would not benefit from 3MDR, and anecdotal evidence is emerging that 3MDR can help people with treatment-resistant PTSD to non-military trauma, but this remains an empirical question and one that needs research to determine the answer.

7.22. The actual mechanism of 3MDR remains unclear; studies with different designs, including dismantling studies, will be required in order to shed more light on this. 3MDR is a complex intervention with a number of different elements and it is not possible to say what is and what is not required at present.

7.23. The number of 3MDR sessions requires more scrutiny. The results of this study suggest that more sessions are likely to be needed for some individuals. It is also unclear as to what the nature of additional session should be. It is possible that additional platform sessions and/or integration sessions would be helpful, with a suggestion that some trauma-focused psychological treatment...
after the platform sessions could be beneficial for some individuals who are now able to engage with treatment in a way they have not been able to before.

7.24. In addition to considering clinical effectiveness, cost-effectiveness work is also required. 3MDR is an expensive intervention; the equipment is costly and it is resource intensive in terms of therapist time and additional support. Therefore, any effectiveness study should include a health economic evaluation to allow informed choices to be made in the future with respect to funding and adoption by clinical services.

7.25. There is also a need for further process evaluation in future research to further evaluate key issues such as optimal levels of support and the characteristics of people with PTSD most likely to benefit from 3MDR.
8: Conclusion

8.1. Although not suitable for all military veterans with treatment-resistant PTSD (specifically PTSD from operational experiences), 3MDR has been shown to reduce symptoms of PTSD and to be well-tolerated by the majority of participants in this study.

8.2. 3MDR has emerging evidence of effectiveness for treatment-resistant PTSD. Further research is now required to determine its true effectiveness and optimal delivery.
9: References


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