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CLINICAL RESEARCH ARTICLE

The psychophysiological response during post-traumatic stress disorder treatment with modular motion-assisted memory desensitisation and reconsolidation (3MDR)

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ABSTRACT

Background: Psychophysiological changes are part of post-traumatic stress disorder (PTSD) symptomatology and can signal emotional engagement during psychological treatment.
Objectives: The aim of this study was to explore psychophysiological responses during multi-modular motion-assisted memory desensitization and reconsolidation (3MDR) therapy. Increased self-reported distress, substantially increased heart rate (HR) and breathing rate (BR) were expected at the start of therapy and predicted to improve over time. Since physical exercise demands during therapy were low, any large HR or BR responses were considered part of the psychophysiological response.
Methods: This study used pooled data collected during a randomized controlled trial of 3MDR, which demonstrated significant improvement as measured by the Clinician Administered PTSD Scale. Whilst attending therapy, HR and BR data, subjective units of distress (SUD) score and phrases to describe feelings whilst exposed to trauma-related images were collected continuously from 37 UK male military veterans with PTSD.
Results: HR and BR were significantly increased throughout all sessions ($p < .01$ for both). Whilst HR was raised slightly remaining on average below 100 beats/minute, BR was increased substantially with average values between 40 and 50 breaths/minute. SUD scores were very high during therapy which concurred with the many negative feelings experienced during therapy sessions. Across the course of the treatment, SUD scores ($p < .01$) and negative feelings were reduced ($p < .001$), and positive feelings have increased ($p < .01$) significantly, reflecting improvements in clinicians assessed PTSD symptoms. Across therapy sessions, HR ($p = .888$) and BR ($p = .466$) responses did not change.
Conclusions: The strong psychophysiological response alongside high levels of self-reported distress and negative feelings is interpreted as high emotional engagement during therapy. A novel finding was the very significant BR increase throughout recorded sessions. Future PTSD research should include BR response to therapy and explore breathing control as a treatment target.

HIGHLIGHTS
• The psychophysiological response during post-traumatic stress disorder treatment with 3MDR in a virtual reality environment.

La respuesta psicofisiológica durante el tratamiento del trastorno de estrés postraumático con terapia modular de desensibilización y reconsolidación de la memoria asistida por movimiento (3MDR)

Antecedentes: Los cambios psicofisiológicos son parte de la sintomatología del trastorno de estrés postraumático (TEPT) y pueden indicar un compromiso emocional durante el tratamiento psicológico.
Objetivos: El objetivo de este estudio fue explorar las respuestas psicofisiológicas durante la terapia multimodular de desensibilización y reconsolidación de la memoria asistida por movimiento (3MDR). Se esperaba un aumento de la angustia autoinformada, un aumento sustancial de la frecuencia cardíaca (FC) y la frecuencia respiratoria (FR) al inicio de la terapia y se predijo que mejoraría con el tiempo. Dado que las demandas del ejercicio físico durante la terapia fueron bajas, cualquier respuesta grande de FC o FR se consideró parte de la respuesta psicofisiológica.
Métodos: Este estudio utilizó datos agrupados recopilados durante un ensayo controlado aleatorio de 3MDR, que demostró una mejora significativa según lo medido por la Entrevista de TEPT Administrada por el Médico. Mientras asistían a la terapia, se recopilaron continuamente datos de FC y FR, puntuación de las unidades subjetivas de angustia (SUD en su sigla en inglés), y frases para describir los sentimientos mientras estaban expuestos a imágenes relacionadas con el trauma; de 37 veteranos militares masculinos del Reino Unido con TEPT.
Resultados: FC y FR aumentaron significativamente a lo largo de todas las sesiones ($p < .01$ para ambas). Mientras que la FC se elevó ligeramente permaneciendo en promedio por debajo de 100 latidos por minuto, la FR aumentó sustancialmente con valores promedio entre 40 y 50

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respiraciones por minuto. Los puntajes de SUD fueron muy altos durante la terapia, lo que coincidió con los muchos sentimientos negativos experimentados durante las sesiones de terapia. A lo largo del tratamiento, las puntuaciones SUD (*p* < .01) y los sentimientos negativos se redujeron (*p* < .001), y los sentimientos positivos aumentaron (*p* < .01) de manera significativa, lo que refleja mejoras en los síntomas de TEPT evaluados por el médico. A lo largo de las sesiones de terapia, las respuestas de FC (*p* = .888) y FR (*p* = .466) no cambiaron.
Conclusiones: La fuerte respuesta psicofisiológica junto con los altos niveles de angustia autoinformada y sentimientos negativos se interpreta como un alto compromiso emocional durante la terapia. Un hallazgo novedoso fue el aumento muy significativo de FR durante las sesiones grabadas. La investigación futura del TEPT debería incluir la respuesta de la FR a la terapia y explorar el control de la respiración como un objetivo del tratamiento.

模块化运动辅助记忆脱敏和再巩固 (3MDR) 治疗创伤后应激障碍的心理生理反应

背景: 心理生理变化是创伤后应激障碍 (PTSD) 症状的一部分, 可以预示心理治疗期间的情绪参与。
目的: 本研究旨在探讨多模块运动辅助记忆脱敏和再巩固 (3MDR) 治疗期间的心理生理反应。预期在治疗开始时自我报告困扰增加, 心率 (HR) 和呼吸率 (BR) 显著增加, 并预计随时间改善。由于治疗期间的体育锻炼要求较低, 任何较大的HR或BR反应都被视为心理生理反应的一部分。
方法: 本研究使用了在3MDR随机对照试验中收集的汇总数据, 由临床用PTSD量表测量, 呈现出显著的改善。在参加治疗的同时, 不断从37名英国男性退伍军人PTSD患者中收集了HR和BR数据, 主观痛苦单位 (SUD) 分数以及描述暴露于创伤相关图像时感觉的短语。
结果: 在所有疗程中, HR和BR均显著升高 (两者均p <.01) 。虽然HR略微升高为平均保持在100次/分钟以下, BR却以40至50次呼吸/分钟的平均值大幅提高。在治疗过程中, SUD评分非常高, 这与治疗期间经历的许多负性感觉相吻合。在整个治疗过程中, SUD评分 (*p*<.01) 和负性感觉减少 (*p*<.001), 积极感觉增加 (*p*<.01), 这反映了临床评估PTSD症状的改善。在整个治疗过程中, HR (*p*= .888) 和BR (*p*= .466) 的反应均未改变。
结论: 强烈的心理生理反应以及高水平的自我报告困扰和负性情绪被解释为治疗期间的高度情感投入。一个新颖的发现是, BR在整个记录的疗程中显著提升。未来的PTSD研究应包括BR对治疗的反应, 并探索将呼吸控制作为治疗目标。

1. Introduction

Post-traumatic stress disorder (PTSD) is associated with a mix of mental and psychophysiological symptoms related to re-experiencing of traumatic events, avoidance, hyperarousal and negative thoughts or feelings. In a thorough systematic review and meta-analysis of psychophysiological responses in PTSD, Pole (2007) found intense distress to be associated with increases in facial muscle contraction levels, heart rate, skin conductance, systolic and diastolic blood pressure. Sinha, Papp, and Gorman (2000) highlighted increased breathing rate in their studies of panic disorder. These psychophysiological responses are proposed to be triggered by an overly sensitive fear network involving cerebral structures such as the pre-frontal cortex, hippocampus, amygdala, and brain stem centres (Sinha et al., 2000). Many studies exploring psychophysiological responses in people with stress, anxiety and/or panic disorders have been carried out at times where participants were exposed to an experimental stress stimulus or a standardized stress-provoking paradigm. For instance, differences in reactive vulnerability between patients and healthy individuals were explored using designed biological and/or cognitive challenges in a laboratory setting (Robinaugh et al., 2020; Siess, Blechert, & Schmitz, 2014). Studies exploring the response to psychological

therapy for PTSD mostly involve pre- and post-measurement of hyperreactivity to trauma-relevant stimuli (Katz et al., 2020; Maples-Keller et al., 2019). Furthermore, studies where participants were exposed to substantial stressful stimuli, typically involved healthy participants. Occasionally, such studies have involved exposure to a real-life, fear-provoking situation. For instance, Schedlowski and Tewes (1992) studied novice compared to experienced skydivers using a portable recording device before, during and after parachute jumps. Not surprisingly, the time just before plane exit and parachute deployment generated the largest self-rated arousal which corresponded with the highest heart rate (HR) and breathing rate (BR) for both groups.

Although there have been studies reporting on the difference in psychophysiological response before and after psychotherapy, it appears that psychophysiological responses during psychotherapy for PTSD have been much less reported in the literature. One study explored psychophysiological responses to combat-related scenarios in virtual reality (VR) to identify sub-threshold PTSD in military service members returned from their deployment (Costanzo et al., 2014). Changes in skin conductivity and heart rate were significant predictors of the Clinician-Administered PTSD Scale (CAPS) score. However, the reported HR

remained between 67 and 69 beats/minute in all conditions: baseline and combat scenarios. BR was not a significant predictor and remained between 16 and 20 breaths/minute. VR combat scenes were also used to compare veterans with and without PTSD in terms of skin conductance reactivity (van 't Wout, Spofford, Unger, Sevin, & Shea, 2017). Both groups showed a similar reduction to repeated presentation of VR combat events. The group with PTSD consistently showed a significantly larger response.

It has been argued that effective treatment of PTSD essentially requires emotional engagement with trauma memories without behavioural avoidance (van Gelderen, Nijdam, & Vermetten, 2018). This emotional engagement ensures activation of the pathological fear network associated with the traumatic event, along with the corrective information that will make the fear network less threatening and anxiety provoking, resulting in extinction (Resick, Suvak, Johnides, Mitchell, & Iverson, 2012). Emotional engagement during treatment should coincide with an increased psychophysiological response which may be exaggerated because of increased reactivity. Zantvoord, Diehle, and Lindauer (2013) concluded in their systematic review that multiple therapeutic approaches used in PTSD treatment resulted in reduced physiological reactivity. Therefore, psychophysiological parameters are of interest when studying treatment effect.

In our recent randomized controlled trial (RCT) of multi-modular motion-assisted memory desensitization and reconsolidation (3MDR), we found 3MDR to significantly improve treatment-resistant service-related PTSD in military veterans (Bisson et al., 2020). This relatively new treatment is based on Virtual Reality Exposure Therapy (VRET) and Eye Movement Desensitization and Reprocessing (EMDR). The 3MDR protocol was delivered by computer in a movement analysis environment. As part of the protocol, HR and BR were continuously monitored and recorded on computer along with self-reported information about participants' feelings and the amount of distress experienced during each cycle of therapy. Therefore, the delivery of 3MDR offered the opportunity to measure psychophysiological response and explore emotional engagement during therapy sessions. The aim was to explore important aspects of the framework proposed by van Gelderen et al. (2018) pertaining to delivery of psychotherapy to patients with treatment-resistant PTSD.

We expected that emotional engagement would be demonstrated by increased self-reported subjective distress together with substantially increased HR and BR. Since physical exercise demands of walking on a treadmill around an average walking speed during therapy were low, any large HR or BR responses were considered part of the psychophysiological response. We further expected that psychophysiological responses would be strongest at the start of therapy and gradually improve over time.

2. Materials and methods

For this study, we pooled all data from participants in our 3MDR RCT (Bisson et al., 2020) to explore change over time in psychophysiological response during 3MDR therapy. The RCT included one arm where participants received immediate therapy. The second arm first received no therapy as a control group and subsequently received 3MDR therapy after a delay of 12 weeks. Data collected during the phase when participants received active treatment from both arms of the study were used. CONSORT guidelines (Rennie, 2001) were followed, and the study was granted approval by the South East Wales Research Ethics Committee (REC reference: 17/WA/0005). Participants were UK military veterans who met DSM5 criteria for PTSD (American Psychiatric Association [APA], 2013) and had previously received trauma focused psychological therapy without loss of PTSD diagnosis or had not engaged in therapy provided. Although the majority were on medication for anxiety, depression, pain and/or various medical conditions, none of these medications have known side-effects affecting heart and/or breathing rate. Structured interviews using the traumatic stress questionnaire by one of the researchers were used to screen for the following exclusion criteria: psychosis, DSM5 severe depressive episode, substance dependence, change in psychotropic medication within one-month, suicidal ideation or intent, and inability to walk for 30–45 minutes on a treadmill. No instances of mania or hypomania were seen during recruitment. All participants provided informed consent before randomization to receive 3MDR therapy immediately or after the delay. The study protocol was delivered over 9 weeks in sessions held once a week (week one for a preparatory meeting, week two for an introductory session with the GRAIL system, six 3MDR therapy sessions and one last meeting for debriefing) by experienced psychological therapists working with Veterans' NHS Wales and Cardiff University. The data collection was carried out during one introductory session (lasting ± 30 minutes) and six therapy sessions (lasting ± 90 minutes).

To deliver 3MDR sessions the Gait Real-time Analysis Interactive Lab (GRAIL, Motekforce Link, Amsterdam, the Netherlands) system at Cardiff University was used which includes an instrumented dual-belt treadmill and synchronized virtual reality (VR) environment using a 180° curved projection screen which covered peripheries with 4 projectors and a surround sound system. All participants wore a safety harness that was fixed to the ceiling by mountaineering rope and carabiners. The 3MDR protocol involved projection of purpose-designed environments and tunnels to walk through

towards self-selected digital pictures integrated into the software. The introductory and therapy sessions were structured identically, using a warmup phase in a calming blue virtual environment, multiple cycles in a red environment while approaching a container-like building opening into a corridor with an image projected at the end of the tunnel (see Figure 1), and a cool down phase in the same calming environment. Participants walked at their self-selected speed and were able to use handlebars for support if desired.

In the therapy sessions, during warmup, self-selected music reminiscent of the traumatic period was played. During cool down favourite music was played to bring the participant back to the here and now. Seven cycles in the red environment were used with projection of self-selected images related to the traumatic experiences. As participants approached each image, they were requested to recount what happened, what they were feeling and what they felt physically as they looked at the image. Thoughts and feelings and where they were felt in the participants' bodies were projected as short phrases onto the screen over the image. After a period of reflection, a dual task was initiated. Participants followed a red ball moving left and right across the screen and called out random numbers that appeared on the red ball. After 30–45 seconds, the image faded to transition to the next cycle or phase. Participants rated their subjective unit of distress (SUD) scores (Wolpe, 1969). Before subsequent sessions, images were updated and/or swapped when the participant and therapist felt that an image no longer provoked sufficient trauma-related anxiety.

The introductory sessions differed in several ways from the therapy sessions. During warm up in the calming blue environment, participants walked at their self-selected pace in the virtual environment. Traumatic experiences were not discussed, and no music was played to avoid stirring memories. This was used as a control condition to determine the physiological response to treadmill walking in terms of a physical exercise. Only three cycles in the subsequent red environment were used. Instead of trauma-related images, three images with a table of words were displayed used for the completion of a neutral, standard, and emotional Stroop test (Stroop, 1935; Williams, Matthews, & MacLeod, 1996). Participants were requested to name the colours of the words projected on the screen for 1 minute per test. The Stroop tests provided a relatively neutral control condition for comparison with the phase of exposure to trauma-related images during therapy sessions.

The purpose-designed software programme running on the GRAIL system included continuous data collection. Data stored digitally included information about timing of transitions between 3MDR cycles and phases, the SUD scores reported by the participants after each 3MDR cycle, the phrases used to describe the projected images and the feelings that these evoked. During all sessions, participants wore a Zephyr Bioharness (Medtronic Zephyr™, Boulder, CO, USA) to measure heart rate (HR) and breathing rate (BR) via a Bluetooth connection to the main system. Good to excellent reliability and validity have been demonstrated in multiple studies (Hailstone & Kilding, 2011; Johnstone et al., 2012; Kim, Roberge, Powell, Shafer, & Jon Williams, 2013). The instrumented treadmill, calibrated yearly against a tachometer, provided data about walking speed and location of foot placement.
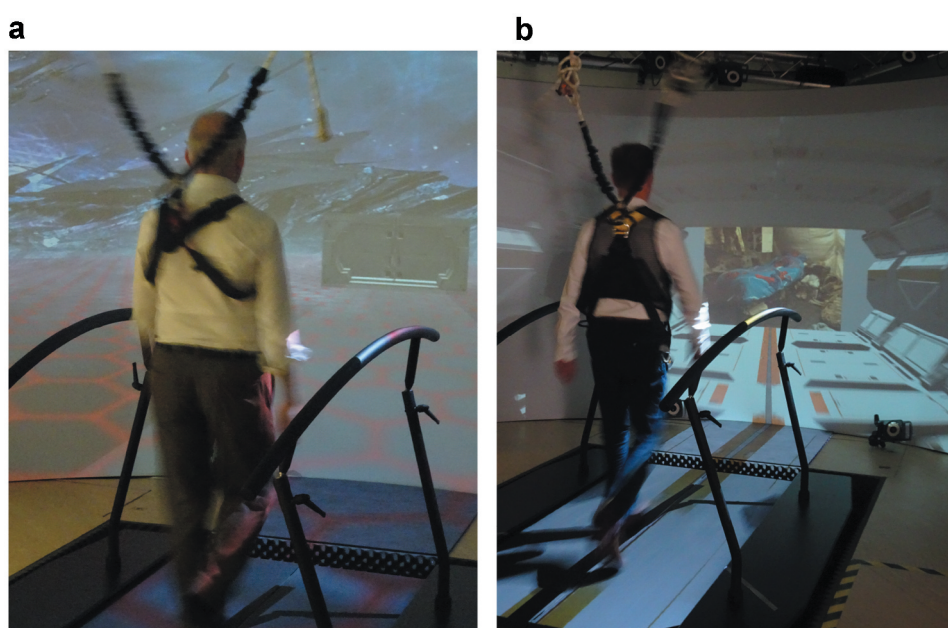
Figure 1. The 3MDR environment. Using virtual reality, a structured environment was presented with harsh features and a container like building (a) opening into a corridor through a set of doors. At the end of the corridor, self-selected pictures were projected ultimately as a 2 m x 2 m image in front of participants (b).

Data stored in two digital files were subsequently analysed using Matlab software (version R2018a, Mathworks®, Natick, MA, USA). For data reduction purposes, walking speed, HR and BR were sampled at 10 time points of a therapy session: at the start and end of warmup, whilst approaching each image as participants were recounting what happened, and at the end of cool down. For the introductory session, 6 time points were used: warmup at the start and end, in the middle of each Stroop test, and at the end of cool down. The average of 10 seconds of data was used at each time point. Further data reduction was applied since no significant changes occurred after completion of the warmup phase. Therefore, the analysis focused on changes between the start and end of warmup for all sessions.

A unique list of 2,151 different phrases used by participants was extracted from all therapy sessions. The valence of these phrases was categorized by three experts based on consensus. They independently reviewed a spreadsheet with phrases in alphabetical order without any other information to ensure blinding. Categories representing negative valences were as follows: Anger; Anxiety; Depression; Guilt; Shame; Maltreated; Revenge; Loneliness; Horror; and Smell. Categories representing positive valences were as follows: Positivity; Motivation; Lucky; Camaraderie. Negativity NOS (not otherwise specified); Physical NOS; and NOS were used where a specific category could not be assigned. The resulting matrix with valences assigned to each unique phrase was used to categorize all phrases within each cycle of the therapy sessions by means of a bespoke algorithm designed in Matlab. For data reduction purposes, valence frequency was calculated per session using this automated approach. Similarly, the average SUD score per session was used for further analysis.

Statistical analysis was carried out using SPSS software (IBM SPSS Statistics 25, Armonk, NY, USA). For this analysis, pooled data were used for all participants from both arms of the RCT to explore changes across the course of treatment. Changes in walking speed, HR, BR, SUD score, frequency of positive and negative feelings were analysed by means of a repeated measures analysis of variance (ANOVA) using therapy session as 6-level factor and start/end of warmup as a 2-level factor. A first order polynomial contrast was used to explore linear change over time. Imputation was used by adding the last available score if participants had not completed all six sessions. Twenty-three participants completed all sessions; three completed 5; six completed 4; one completed 2; and four completed 1 session. In a separate analysis, the introductory session was compared to the first therapy session by means of a two-way ANOVA. Assumptions for normal distribution and equal variances were checked. Significance level was set at 0.05. Descriptive analysis was used to summarize phrase valence data.

3. Results

Out of a total of 42 UK male military veterans participating in both arms of the RCT, psychophysiological data from 37 were available for further analysis. The number available for psychophysiological analysis was reduced because five participants did not attend the therapeutic sessions after randomization. The average age for the reduced group was 41.5 ± 10.7 years with a range of 28 to 67 years.

The average walking speed used by the group during sessions was 0.99 ± 0.21 m/s. Since sessions lasted about 90 minutes the total distance walked ranged between 4.8 and 6 km. Although participants could request changes to treadmill speed this hardly ever occurred. Walking speed did not significantly change over the therapy sessions ($F_{5,180} = 1.514$; $p = .213$) and there was no significant difference between the introductory and the first therapy sessions ($F_{1,36} = 0.241$; $p = .627$). See Figure 2.

SUD scores (Figure 3) were significantly reduced from first to last therapy session ($F_{1,36} = 10.485$; $p < .01$). Visit one average SUD score was close to 7 representing 'Starting to freak out, on the edge of some definitely bad feelings. You can maintain control with difficulty'. The final session average between 5 and 6 indicated participants being moderately upset to feeling bad.

The Bioharness sensor data revealed that heart rate increased significantly between the start and the end of warmup ($F_{1,34} = 31.203$; $p < .01$) although the change was not large (see Figure 4). On average, HR remained below 100 beats/minute. Two participants remained below 80 beats/minute during all sessions; 17 remained below 100; 13 remained below 120; and 5 (14%) on occasion had an HR somewhat higher than 120. This response did not change significantly across the therapy sessions ($F_{5,170} = 0.245$; $p = .888$) and was not different between the introductory session and the first therapy session ($F_{1,34} = 0.021$; $p = .884$).

Breathing rate increased significantly between the start and the end of warmup ($F_{1,36} = 95.214$; $p < .01$) and this change was substantial (see Figure 5). On average, BR increased from a resting rate somewhere between 12 and 20 breaths/minute to a rate between 40 and 50 during sessions. Two participants always kept their BR below 20; three had a BR between 20 and 30; two had a BR between 30 and 40; and 30 (81%) typically had a BR higher than 40. In several cases, BR was well above 40 which was quite unexpected. This response did not change significantly across the therapy sessions ($F_{5,180} = 0.854$; $p = .466$) and was not different between the introductory session and the first therapy session ($F_{1,36} = 0.966$; $p = .332$).

Table 1 lists the frequency with which phrases within a valence category were used across all sessions by all participants. Phrases with a negative valence occurred 67.9% of the time. Most frequent were phrases represen
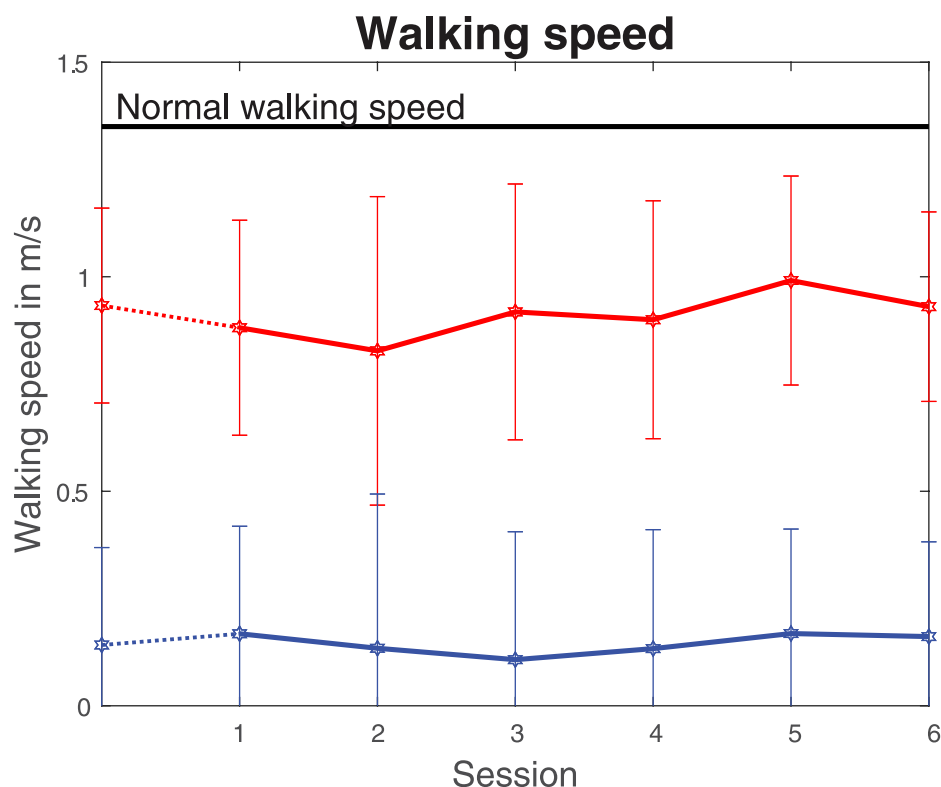
Figure 2. Walking speed at the start when the treadmill was still being ramped up from standstill to preferred walking speed (blue); and at the end of the warmup phase with steady state walking (red). Means and standard deviations for the introductory session (0) and the therapy sessions (1–6) are displayed. The change over time was not significant ($p = .213$). Average, normal adult walking speed is included as a black line to highlight the relatively slow speed used by participants.
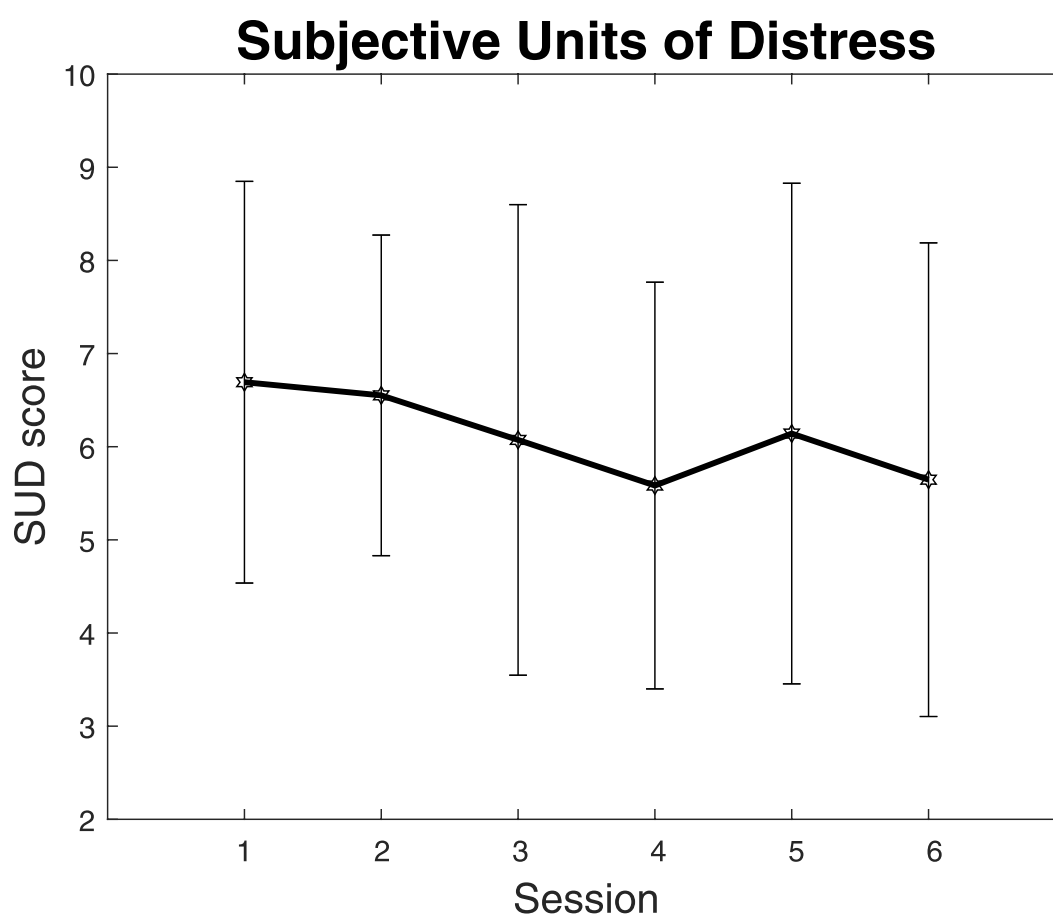
Figure 3. SUD scores (mean and standard deviations) measured across the therapy sessions. The reduction in score over time was significant ($p < .01$).
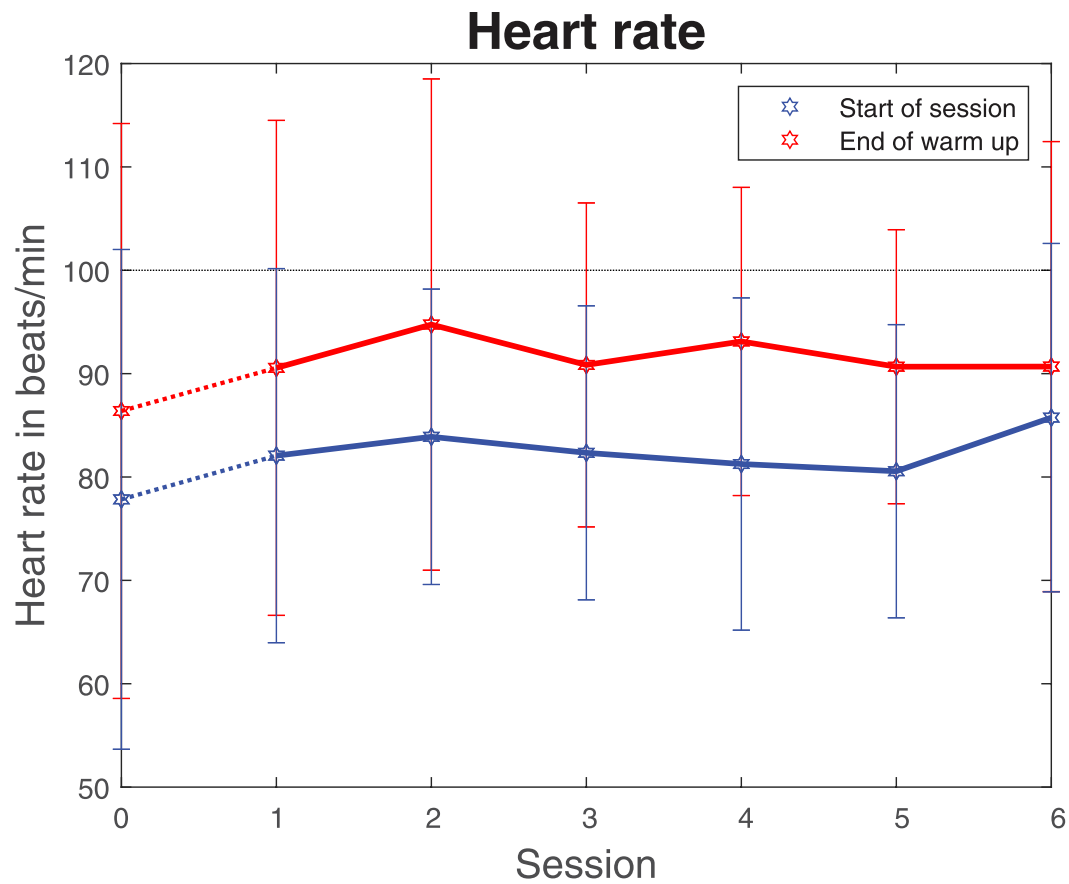
Heart rate

Figure 4. Heart rate at the start of the warmup phase (blue) and at steady state walking (red). Means and standard deviations for the introductory session (0) and the therapy sessions (1–6) are displayed. The change over time was not significant ($p = .888$). The line representing a heart rate of 100 beats/min was added to indicate a response to mild exercise.
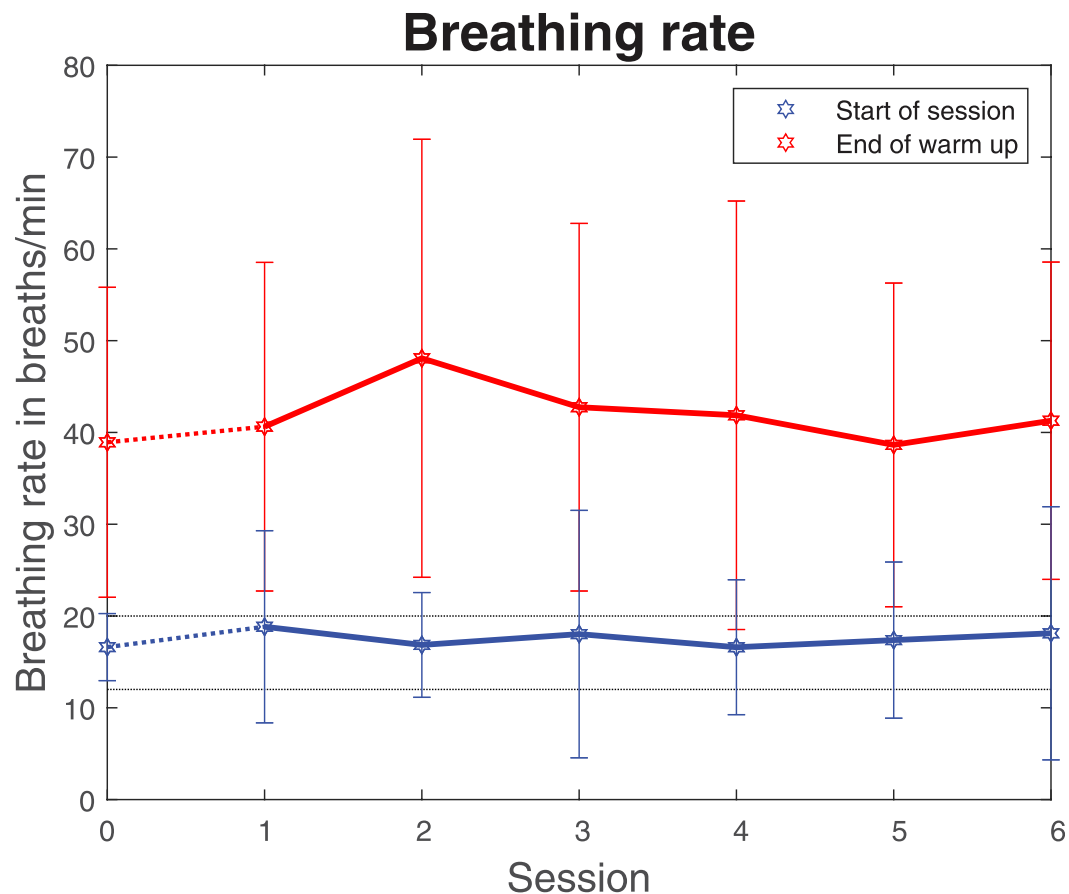
Breathing rate

Figure 5. Breathing rate at the start of the warmup phase (blue) and at steady state walking (red). Means and standard deviations for the introductory session (0) and the therapy sessions (1–6) are displayed. The change over time was not significant ($p = .466$). The dotted line representing a breathing rate of 12 and 20 breaths/min were added to indicate the range of rate at rest in various postures.

Table 1. Frequency and percentage at which phrases within a valence category was used across all sessions by all participants.

Valence	Frequency	Percentage
• Anger	619	12%
• Anxiety	1245	24%
• Depression	519	10%
• Guilt	290	5%
• Horror	16	< 1%
• Loneliness	6	< 1%
• Maltreated	4	< 1%
• Revenge	47	1%
• Shame	38	1%
• Smell	62	1%
• Negativity NOS	744	14%
Negative valances total	3590	67.9%
• Camaraderie	27	< 1%
• Lucky	63	1%
• Motivation	23	< 1%
• Positivity	914	17%
Positive valences total	1027	19.4%
Physical NOS	371	7%
NOS	298	6%
Total	5286	
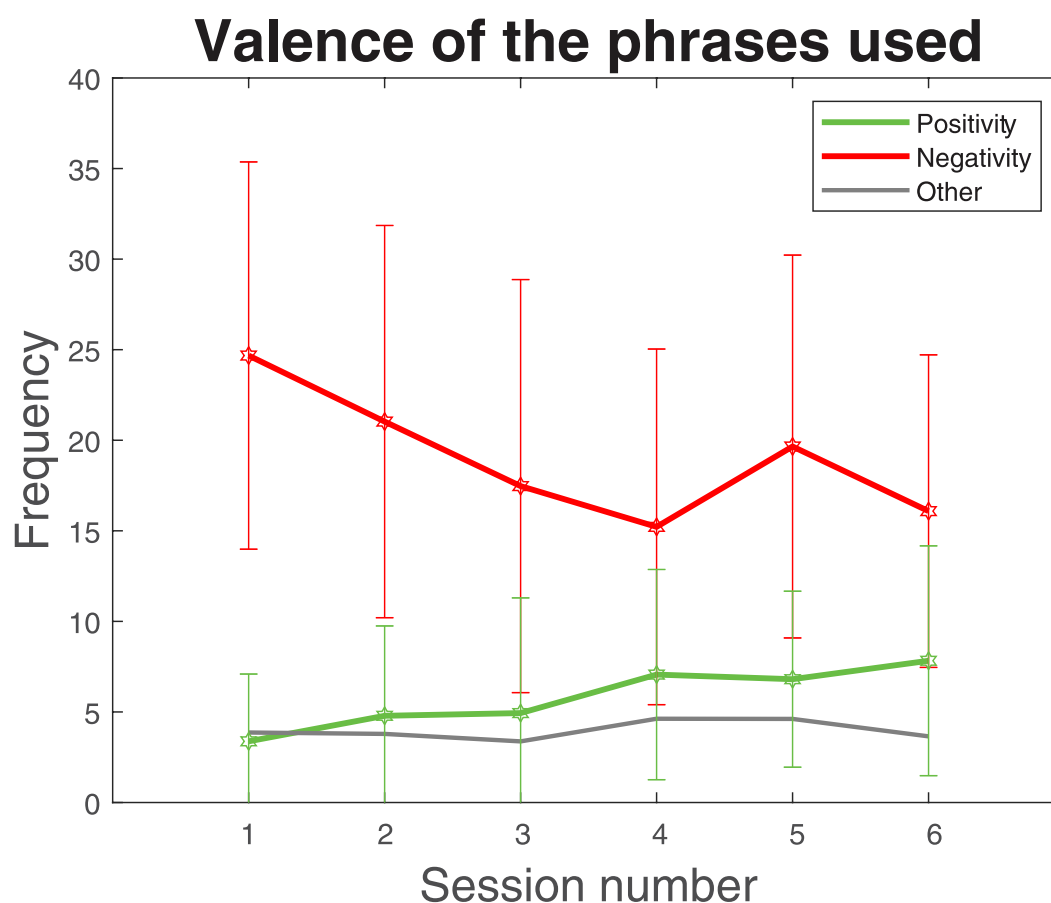
Figure 6. Negative and positive valences of phrases used during therapy session are shown as the mean and standard deviation of the frequencies each occurred across the sessions. The reduction in frequency of negative valence over time was significant ($p < .001$). The increase in frequency of positive valence over time was also significant ($p < .01$). The grey line indicates the frequencies in the use of non-specific phrases.

tative of anxiety (24%). Anger (12%) and depression (10%) were substantial categories as well. Phrases with a positive valence occurred 19.4% of the time. Figure 6

illustrates the change in frequency of phrases with a negative and positive valence as therapy progressed. The reduction in phrases with a negative valence was

significant ($F_{1,36}$ = 18.733; p < .001), mirroring SUD score changes. The increase in phrases with a positive valence was also significant ($F_{1,36}$ = 11.842; p < .01).

About half of the cases with a referral to a physical feeling were classed as anxiety, such as 'adrenaline all over body', 'chest tight', 'cold sweats', 'dry throat', 'hair standing on end', 'heart pounding', 'knot in stomach', 'tense in body', 'tension in hands and arms', 'tight jaw', 'weak in the knees'. Non-specific physical sensations referred to 'aching shoulders', 'gritty eyes', 'headache', 'itchy legs and hands', 'nausea', 'pain in stomach', 'pressure behind eyes' etc. There were 42 phrases mentioning the heart (2%) but only half of these referred to heart beating; and 21 phrases mentioning breathing (1%) such as 'short of breath', 'shallow breathing', 'hard to breathe', and 'easier breathing'.

4. Discussion

The aim of this study was to explore the psychophysiological response during PTSD therapy by means of 3MDR. Subjective distress was substantial during therapy as demonstrated by the high SUD scores. Self-reported distress concurred with the many negative feelings experienced during therapy sessions. HR and BR were both significantly increased throughout sessions. Whilst heart rate was raised only slightly, breathing rate was increased significantly. The substantial increases we observed in the majority of participants were not expected. Bioharness sensor data was reviewed but no abnormalities in sensor performance were detected. Furthermore, reports in the literature related to its excellent reliability and validity against the gold standard (Kim et al., 2013) provided reassurance that this was not a methodological issue.

As previously published, significant improvement through 3MDR therapy was demonstrated by the CAPS5 (Bisson et al., 2020). A significant reduction in SUD scores from the first to last therapy session is consistent with these results. Participants updated their images that they were confronted with in sessions as soon as an image no longer provoked marked trauma-related anxiety rated by the SUD score replacing it with a new high impact image. Therefore, the overall reduction in perceived distress would have likely been more profound than is made obvious in Figure 4. Also, the decreased frequency of phrases with negative valence (most prominently anxiety, anger, and depression) and increased frequency of phrases with positive valence signalled the same pattern. HR and BR did not demonstrate changes over the course of therapy. BR remained particularly high throughout all phases, cycles, and visits. Had more treatments than six been offered, it is conceivable that BR may have been finally reduced.

In this study, stress levels were very high as indicated by the mean and standard deviation of SUD scores. SUD scores of 9 and 10 were regularly encountered, indicative of severe feelings of distress. However, the average HR remained between 90 and 100 beats/min during sessions. Given the exceptionally high BR response to perceived distress, a more pronounced HR response was expected. The parachute jumping experiment by Schedlowski and Tewes (1992) reported HR increases to 150–165 beats/min. Costanzo et al. (2014) measured HR in military service members with sub-threshold PTSD whilst they were exposed to VR combat events. Their results for HR varied between 68.86 ± 9.75 (baseline) and 67.33 ± 10.51 beats/min (Convoy 1). It is likely that participants were seated behind a screen. YongWoo et al. (2012) demonstrated that undisturbed walking at normal speed on a treadmill produced a HR of 97.8 ± 9.1 beats/min in 12 healthy individuals aged 35.4 ± 2.7 years: an age close to our group of participants. It therefore seems that HR in this study is related to the walking activity as a physical exercise rather than perceived distress.

Breathing rate is known to increase under stress generated by demanding physiological, pathophysiological, or psychological stimuli (Tipton, Harper, Paton, & Costello, 2017). In the study by Costanzo et al. (2014) using VR combat scenarios, BR results were not significant and varied between 16.34 ± 2.68 and 19.67 ± 3.18 breaths/min (Convoy 2). BR increases in this same range were found to correlate substantially with subjective anxiety (Papp et al., 1988), a consistent finding in laboratory studies exploring panic disorder (Sinha et al., 2000). However, an average BR hovering between 40 and 50 is exceptionally high and has not been reported before. There were some cases where BR was as high as 80 and above. A thorough search of the literature revealed very limited comparative studies since many did not quantify BR increases. Most interesting was the parachute jumping experiment by Schedlowski and Tewes (1992) which reported increased breathing rates for both the novice and experienced groups over multiple study phases with highest levels between 30 and 35 breaths/min. A further search of physical exercise studies provided some references reporting on maximal breathing rates. A study by Blackie et al. (1991) using a cycle ergometer reported breathing rates at maximal exercise of 36.1 ± 9.2 breaths/min. Witt et al. (2006) studied BR during various physical activities. Their results included standing: 16.2 ± 4.6; slow walking: 22.2 ± 7.3; jogging: 32.4 ± 6.5; and maximal running: 51.7 ± 13.2 breaths/min. The 3MDR protocol involves walking on a treadmill. However, the level of physical exercise was very low since, on average, participants walked slower than the normal, average preferred walking speed for male adults (Burnfield & Perry, 2010). Under normal circumstances, such a mild exercise would not provoke even a moderate exercise response

and a breathing rate of around 20–22 breaths/min would be expected (Witt et al., 2006). It is also important to note that at the start of all sessions, the baseline BR was well within the expected normal range of 12–20 breaths/min (see blue line in Figure 5) which was measured as walking on the treadmill was first started. Furthermore, physical exercise is expected to affect HR more than BR (Vai, Bonnet, Ritter, & Pioger, 1988). However, HR responses were modest in this study, whilst BR responses were much more salient. Although not recorded in detail, many participants in this study were perceived to be unfit. It is a limitation of the study that participants did not undergo a detailed physical examination before enrolment. Instead, we asked participants to confirm that they were able to walk for 30–45 minutes. However, lack of fitness does not seem to explain observed responses since the HR response was so modest in most, indicative of very mild physical exercise demands. Furthermore, none of the participants were on beta-blockers or any other medication that would lower heart rate as a side-effect. It therefore seems reasonable to conclude that the exceptionally high BR which was found in 81% of the participants was strongly triggered by stress-related arousal.

These observations are inconsistent with a unitary stress response where all psychophysiological parameters increase in concert in preparation for fight or flight (Goldstein, 2010). Although both HR and BR rate increases were significant, the small size of the response for HR was surprising in the presence of a very large increase in BR. Specificity of the stress response has been proposed which is dependent on the stressor as well as to the individual's perceptions of and ability to cope with the stressor (Goldstein, 2010). Differentiation between the respiratory and cardiac increases based on stress response specificity may explain why parachute jumping resulted in relatively large HR increases compared to BR increases (Schedlowski & Tewes, 1992). By contrast, exposure to 3MDR therapy resulted in large BR increases compared to modest HR increases. These differences may be explained by an increased physiological reactivity to stress in PTSD patients compared to healthy participants. The fact that study participants were veterans with treatment-resistant PTSD may be relevant in this context, but this would have to be confirmed by further research.

It is considered unlikely that this response is specific to 3MDR therapy. The same HR and BR response occurred in the introductory session as observed in the therapy sessions. The introductory visit did not involve confrontation with trauma-related images and no participants' music was played. Furthermore, participants were distracted by three Stroop tests. However, the psychophysiological response was very much the same. In the introductory and all therapy sessions, this response started shortly after the warmup phase was initiated and continued all the way to the end of cool down. Participants therefore demonstrated a generic response that may be considered indicative of their emotional engagement (van Gelderen et al., 2018). During post-treatment interviews, the 3MDR environment was described by participants as very, very immersive. The fact that participants knew that the 3MDR environment would be used for their PTSD treatment, in anticipation may have triggered the same psychophysiological response during the introductory session as seen during therapy. This generic response to the virtual reality setup may also explain why psychophysiological responses did not change even though the CAP5 as primary outcome measure, reported by Bisson et al. (2020), had demonstrated a significant improvement. Furthermore, the fact that the images were regularly updated when a participant and therapist agreed that an image was no longer beneficial for therapy could have resulted in this lack of change.

An increased BR in the range of 20–100 breaths/min is also known clinically as tachypnoea (Tipton et al., 2017) and/or hyperventilation. For participants to be able to hyperventilate for a period of 90 minutes without experiencing major symptoms, it is unlikely that they were hyperventilating in the true sense of the term. Participants used phrases during therapy that could be related to hyperventilation symptoms, such as feeling lightheaded, dizzy, weak, tight chested, heart pounding, winded, dry mouth, tingling, and cramps. However, occurrences were rare. Therapists did on occasion agree to a break in proceedings and offered a drink, but no one needed medical interventions indicative of hyperventilation syndrome. By implication, this means breathing was fast and shallow as in panting or tachypnoea (Tipton et al., 2017) so that hypocapnia (Ley, 1985) seen in hyperventilation was avoided. To some extent, walking will have contributed to control hypocapnia since physical exercise increases blood CO_2 levels, although more vigorous exercise would be more beneficial.

Considering these results, it is striking that Pole (2007) in her systematic review of psychophysiological responses in PTSD did not report any studies exploring the BR response. Nicolò, Massaroni, and Passfield (2017) have argued that BR measurement received little consideration to date in the field of sport and exercise as well as in the clinical field, despite being recognized as a vital sign. Zaccaro et al. (2018) in their systematic review discussed how breathing is intimately linked with mental functions. They reported that slow breathing techniques promote autonomic alongside central nervous system activity modifications reflected in psychological/behavioural changes such as relaxation, and reduced symptoms of arousal, anxiety, depression, and anger. The results from this study highlight the important role of breathing in the psychophysiological response. An obvious limitation

of this study is that all participants were men. Consequently, any generalization of these findings to women is not possible at this stage. Based on these results, we do conclude that measurement of BR should be conducted in conjunction with other physiologic measures in more studies so that its specific importance can be more fully understood.

5. Conclusion

Psychophysiological data collected during a high-quality RCT demonstrated a strong BR response alongside high levels of self-reported distress. Our interpretation is that high emotional engagement was present during therapy. A novel finding was the large amount with which breathing rate increased. This occurred throughout recorded sessions whilst heart rate increases were much more modest though significant. Breathing rate and experimental breathing interventions should be included in future research of PTSD treatment. Furthermore, it may be valuable to explore breathing control as a treatment target in much more detail.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

The data that support the findings of this study are available from the corresponding author, RvD, upon reasonable request. The data are not publicly available due to restrictions related to university protocol.

Institutional review board approval information

The study with IRAS project ID: 213400 was reviewed under the REC reference number 17/WA/0005 by the South East Wales Research Ethics Committee and approval was obtained before data collection was commenced.

Informed consent/patient consent statement

Informed consent was obtained from all individual participants included in the study. Figure 1 provides images of collaborating researchers of the study in a way that does not reveal their identity. Their consent for publication was obtained.

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