

# Trauma, treatment and Tetris: video gaming increases hippocampal volume in male patients with combat-related posttraumatic stress disorder

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**Background:** Tetris has been proposed as a preventative intervention to reduce intrusive memories of a traumatic event. However, no neuroimaging study has assessed Tetris in patients with existing posttraumatic stress disorder (PTSD) or explored how playing Tetris may affect brain structure. **Methods:** We recruited patients with combat-related PTSD before psychotherapy and randomly assigned them to an experimental Tetris and therapy group ( $n = 20$ ) or to a therapy-only control group ( $n = 20$ ). In the control group, participants completed therapy as usual: eye movement desensitization and reprocessing (EMDR) psychotherapy. In the Tetris group, in addition to EMDR, participants also played 60 minutes of Tetris every day from onset to completion of therapy, approximately 6 weeks later. Participants completed structural MRI and psychological questionnaires before and after therapy, and we collected psychological questionnaire data at follow-up, approximately 6 months later. We hypothesized that the Tetris group would show increases in hippocampal volume and reductions in symptoms, both directly after completion of therapy and at follow-up. **Results:** Following therapy, hippocampal volume increased in the Tetris group, but not the control group. As well, hippocampal increases were correlated with reductions in symptoms of PTSD, depression and anxiety between completion of therapy and follow-up in the Tetris group, but not the control group. **Limitations:** Playing Tetris may act as a cognitive interference task and as a brain-training intervention, but it was not possible to distinguish between these 2 potential mechanisms. **Conclusion:** Tetris may be useful as an adjunct therapeutic intervention for PTSD. Tetris-related increases in hippocampal volume may ensure that therapeutic gains are maintained after completion of therapy.

## Introduction

Recent work has provided evidence for the utility of the visuospatial video game Tetris as an early therapeutic intervention for posttraumatic stress disorder (PTSD).<sup>1-3</sup> Holmes and colleagues have shown that playing Tetris directly after trauma exposure can reduce subsequent intrusive memories of the traumatic event, and they have demonstrated the efficacy of this “cognitive vaccine” in both experimental<sup>1</sup> and real-world settings.<sup>2-4</sup>

Following exposure to an event, the memory trace of that event must be consolidated into long-term memory for it to be accessible for later recall.<sup>5</sup> Shortly after the event, the memory trace remains in a labile state as it is consolidated, and it is susceptible or vulnerable to interference.<sup>6</sup> Performing an unrelated task while the memory for an event is in a

labile state can reduce subsequent retrieval.<sup>7</sup> In addition, it has been proposed that following reactivation, a memory again enters a labile state and must be reconsolidated into long-term memory.<sup>8</sup> During this reconsolidation process, the memory trace is also vulnerable to interference. Holmes and colleagues<sup>1</sup> have proposed that by completing a demanding visuospatial task during memory consolidation or reconsolidation for a traumatic event, the memory trace is weakened because of competition for the cognitive resources required for consolidation.

To date, work using Tetris as an intervention has focused mainly on attempting to disrupt consolidation of the traumatic memory within the first 6 hours after the trauma exposure,<sup>1-3</sup> or reconsolidation of the traumatic memory the next day.<sup>8</sup> However, playing a video game in the direct aftermath of a traumatic event is neither practical nor possible in

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every case. It is estimated that approximately 8 million adults have PTSD in the United States alone.<sup>9</sup> As such, interventions for those who are already experiencing posttraumatic symptoms are sorely needed.

One study to date has assessed a Tetris intervention in people with existing PTSD.<sup>4</sup> In this study, specific intrusions were targeted based on the concepts of “concurrent task interference and memory reconsolidation.” After a reminder for a specific intrusive memory, patients played 25 minutes of Tetris. The authors found that after completion of the study, the frequency of targeted intrusions was lower than that of nontargeted intrusions. In the current study, we investigate the utility of Tetris as an adjunct therapeutic intervention for people with current PTSD.

Current therapeutic interventions for PTSD have a number of limitations related to response rates and long-term efficacy. A significant minority of people with PTSD will not show significant improvement in symptoms directly following therapy, with rates of nonresponders estimated to be as high as 35% to 50% in some studies.<sup>10–12</sup> In addition, the long-term prognosis for PTSD is poor: a majority of people continue to experience symptoms for months or years after initial diagnosis, and a substantial number never fully recovers.<sup>13</sup> As such, there is a significant need for additional therapeutic interventions that may act as an adjunct to traditional psychotherapy for nonresponders and to ensure the long-term maintenance of therapy-related gains for responders.

The most widely used and most effective interventions for PTSD are psychotherapies such as trauma-focused cognitive behaviour therapy (CBT) and eye movement desensitization and reprocessing (EMDR) therapy. These therapies target memories of the traumatic event, along with the person’s cognitive and emotional interpretation of the event. Therapy with EMDR is particularly interesting, because it differs from other psychotherapies by incorporating a visuosensory attentional component.<sup>14</sup> There are some inconsistencies in the literature regarding EMDR, particularly the therapeutic contribution of the visuosensory component:<sup>15</sup> although reviews of studies comparing trauma-focused CBT and EMDR have failed to demonstrate increased efficacy for one over the other,<sup>10,15</sup> separate reviews have provided evidence that the addition of eye movements results in significant improvements to treatment outcomes.<sup>16,17</sup> As such, although EMDR is a common therapeutic intervention for the treatment of PTSD, the precise mechanisms underlying its efficacy remain somewhat unclear.

In the current study, we explored the use of Tetris as an adjunct to EMDR. Each EMDR session consisted of selecting a traumatic memory to work on. Given the visuosensory attentional component of EMDR, we considered that Tetris might complement EMDR better than other psychotherapeutic interventions, such as CBT.

At the neuroanatomical level, adult PTSD populations are characterized by smaller volumes in the hippocampus and in prefrontal regions, including the ventromedial prefrontal cortex and the anterior cingulate cortex.<sup>18–20</sup>

The hippocampus is hypothesized to play a key role in PTSD symptomatology: smaller hippocampal volumes have been associated with increased risk and poorer prognosis in

PTSD, and with poorer prognosis.<sup>21–25</sup> In addition, increases in grey matter volume in the hippocampus have been observed in response to psychological therapy, including EMDR<sup>26,27</sup> and pharmacological interventions, and increases in hippocampal volume have been linked to improvements in memory.<sup>28</sup>

Training studies have demonstrated that increases in hippocampal volume can be produced with a wide variety of interventions,<sup>29,30</sup> including video-gaming interventions.<sup>31</sup> As such, we hypothesized that the video-gaming intervention Tetris would increase hippocampal volume, which would in turn reduce PTSD symptomatology.

Smaller prefrontal regions have also been commonly observed in people with PTSD.<sup>18–20</sup> Prefrontal regions have also been shown to increase in response to video-gaming interventions.<sup>31</sup> We therefore hypothesized that prefrontal regions in PTSD populations would also increase in response to therapeutic interventions, although the majority of relevant work in neuroplasticity and PTSD has demonstrated effects in the hippocampus rather than the prefrontal regions.

In the current study, we investigated the structural and behavioural effects of a Tetris intervention in people with PTSD who were undergoing psychotherapy, using a prospective design. We recruited people with combat-related PTSD and assessed them before and directly after EMDR therapy, as well as at follow-up, approximately 6 months later. We proposed that playing Tetris after therapy while the reactivated traumatic memory was in a labile state would weaken reconsolidation and aid recovery.<sup>8</sup> It should be noted that playing Tetris has been shown to reduce the vivid, intrusive elements of a traumatic memory, but not of a declarative memory.<sup>1</sup> As such, we expected that Tetris would not affect memory of the therapy sessions, or interfere with the clinical efficacy of EMDR. In addition, spatial memory training and video gaming have been linked to increases in hippocampal volume,<sup>31</sup> and increases in hippocampal volume have been associated with improvements in memory and reductions in symptoms in PTSD.<sup>32</sup> As such, we expected that Tetris would aid in recovery from PTSD by weakening the memory of the traumatic event, and by increasing hippocampal volume. We hypothesized that the Tetris group would show increases in hippocampal volume and reductions in symptoms — directly after completion of therapy and at follow-up.

## Methods

### *Participants*

We recruited 40 participants with combat-related PTSD from the German Federal Armed Forces before they started therapy. All participants were inpatients at the German Military Hospital, Berlin, Germany. All participants were male and had been deployed overseas to areas of conflict. For inclusion criteria, participants were screened by clinical psychologists and psychiatrists for the presence of mission-related trauma within the preceding 2 years and for a current diagnosis of PTSD according to ICD-10 criteria. For exclusion criteria, participants were screened for current or previous comorbid

psychosis or substance abuse, use of psychotropic medication, a history of concussion or traumatic brain injury, and contraindications for MRI. Patients were assessed for inclusion and exclusion criteria and then randomly assigned to the experimental Tetris group ( $n = 20$ ) or the control group ( $n = 20$ ). The local ethics committee of Charité University Clinic (Berlin, Germany) approved the study, and we obtained written informed consent from each participant before they entered the study, in line with the declaration of Helsinki.

Participants in both groups completed EMDR therapy.<sup>14,33</sup> Participants in the control group completed EMDR therapy only, and participants in the experimental Tetris group also played the video game Tetris for 60 minutes per day from the start of therapy to completion, approximately 6 weeks. After completion of therapy, all participants returned for neuroimaging and questionnaire assessment. Approximately 6 months after completion of therapy, participants also completed the questionnaire assessment only. Four participants — 2 in the Tetris group and 2 in the control group — did not complete the 6-month follow-up assessment.

### *Psychotherapy intervention*

All participants completed EMDR therapy — one of the most common therapeutic interventions for PTSD<sup>34</sup> and known to effectively reduce symptoms in a majority of individuals directly after completion of therapy.<sup>14,15,33</sup> Psychotherapists and psychotherapy-specialized senior psychiatrists performed the EMDR in single sessions. Treatment was conducted according to standard EMDR protocol. A 1-week stabilization and preparation phase was followed by a 4-week exposure phase, with an average of 2 sessions per week for 60 to 90 minutes each. Participants completed a mean of  $7.2 \pm 1.8$  sessions over approximately 6 weeks (duration  $39.9 \pm 4.8$  d). When the number of sessions was not available from the clinical records ( $n = 3$ ), we used participant self-report data. Each EMDR session consisted of selecting a memory to work on. The selected memory was then reactivated, during which time the individual attended briefly to certain elements of the memory while simultaneously engaging in a periodic set of eye movements by focusing on a moving visual stimulus controlled by the therapist.

### *Tetris intervention*

Participants in the Tetris group were given a Nintendo DS XL console and the computer game Tetris. Participants were asked to play for 60 minutes per day. Participants reported playing a mean of  $61 \pm 14.6$  minutes per day (data not available for 2 participants) and missing a mean of  $1 \pm 1.2$  day (data not available for 2 participants). On days that participants completed an EMDR therapy session, they were required to play Tetris within 6 hours after they completed therapy.

### *Questionnaires*

To assess participants' duration of military deployment and their experiences during deployment, we asked them to com-

plete a German version of the Combat Experiences Scale — a 33-item questionnaire that assesses the type and frequency of combat-related events during military deployment<sup>35</sup> — and a study-specific questionnaire that included items about the number and duration of military deployments.

To assess psychological symptoms, participants also completed German versions of the following self-report questionnaires before each neuroimaging session: the Posttraumatic Diagnostic Scale (PDS), the Beck Depression Inventory II (BDI-II) and the State-Trait Anxiety Inventory (STAI).

The PDS<sup>36,37</sup> is designed to aid in the diagnosis of PTSD and assess symptom severity. As part of the PDS, respondents rate 17 items representing the main symptoms of PTSD they have experienced in the preceding 30 days using a 4-point scale, ranging from 0 ("not at all or only 1 time") to 3 ("5 or more times a week or almost always").

The BDI-II<sup>38,39</sup> is a 21-item inventory that assesses the characteristic behaviours and symptoms of depression participants experienced in the preceding 2 weeks using a 4-point scale, ranging from 0 ("I do not feel sad") to 3 ("I am so sad or unhappy I can't stand it").

The STAI<sup>40,41</sup> consists of 2 forms that assess state anxiety, experienced currently (Form X-1), and trait anxiety, experienced in general (Form X-2). In the current study, we used the trait anxiety subscale of the STAI (Form X-2) because we were interested in assessing changes in enduring states of anxiety and stress rather than temporary ones. In Form X-2, individuals rate 20 statements describing emotions of stress and worry using a 4-point scale, ranging from 1 ("almost never") to 4 ("almost always").

### *MRI scanning procedure*

We acquired structural images using a 3 T Magnetom Tim Trio MRI scanner system (Siemens Medical Systems) and a 12-channel radiofrequency head coil. We obtained the images using a 3-dimensional  $T_1$ -weighted magnetization-prepared gradient-echo (MPRAGE) sequence based on the Alzheimer's Disease Neuroimaging Initiative protocol ([www.adni-info.org](http://www.adni-info.org); repetition time 2500 ms, echo time 4.77 ms, inversion time 1100 ms, acquisition matrix  $256 \times 256 \times 176$ , flip angle  $7^\circ$ , voxel size  $1 \times 1 \times 1$  mm<sup>3</sup>).

### *MRI data analysis*

We processed structural data using the computational anatomy toolbox (CAT12; <http://dbm.neuro.uni-jena.de/cat/>) and statistical parametric mapping (SPM12; <http://www.fil.ion.ucl.ac.uk/spmb>) with default parameters running on MATLAB 9.1 (Mathworks). We used voxel-based morphometry to estimate the local amount, or volume of grey matter. Voxel-based morphometry is a neuroimaging analytic technique that allows the investigation of focal differences in brain anatomy based on statistical parametric mapping of structural images. It involves bias correction, tissue classification and affine registration. We normalized images to the Montreal Neurological Institute (MNI) space using the ICBM152 template<sup>42</sup> and segmented them into grey matter,

white matter and cerebrospinal fluid using default parameters. We applied modulation to preserve the volume of a particular tissue within a voxel by multiplying voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step. We smoothed images with a full width at half maximum (FWHM) kernel of 8 mm.

We computed a whole-brain voxel-wise factorial analysis. We included age and total intracranial volume as covariates of no interest and applied an absolute grey matter probability threshold of 0.2 (CAT12 manual, <http://dbm.neuro.uni-jena.de/cat12/CAT12-Manual.pdf>). We thresholded the resulting maps at  $p < 0.001$  at the voxel level and cluster-extent thresholded them at 100 voxels per cluster to control for type I error.

We also conducted region-of-interest (ROI) analysis in the hippocampus, a region commonly implicated in adult PTSD.<sup>19,25</sup> We defined a bilateral anatomic hippocampal mask for the hippocampus using the anatomic automatic labelling (AAL)<sup>43</sup> template. We defined a PTSD-specific hippocampal mask using the hippocampal cluster identified in a previous meta-analysis of whole-brain neuroimaging studies.<sup>20</sup> We used the Region-of-Interest Extraction (REX) toolbox to extract grey matter volumes from the identified clusters and then entered the values for extracted volumes into repeated-measures analysis of variance.

We also assessed the relationship between increases in hippocampal volume and subsequent reductions in symptoms. We calculated change in the hippocampus by using the cluster identified in the whole brain analysis and subtracting pre-therapy from post-therapy hippocampal grey matter volumes; positive values indicated increases in hippocampal volume following completion of therapy. We also calculated change in symptoms by subtracting follow-up PDS, BDI-II and STAI scores from post-therapy scores; negative values indicated a decreases in symptoms from completion of therapy to follow-up. We then correlated these change scores separately for each group.

## Results

### Participants

The Tetris and control groups did not differ by age, sex, duration of military deployment, combat exposure, number of EMDR sessions or interval between assessments (Table 1).

### Neuroimaging analyses

Whole-brain analysis revealed a significant increase in grey matter volume in a cluster in the right hippocampus after therapy in the Tetris group ( $k = 150$ ,  $x = 27$ ,  $y = -33$ ,  $z = -3$ ,  $p < 0.001$  at the voxel level; and  $k > 100$ , non-isotropic smoothness corrected at the cluster level; Table 2 and Fig. 1), compared with the control group.

As well, ROI analysis of the hippocampus revealed a significant group  $\times$  time interaction. Compared to the control group, we found larger volumes in the Tetris group after therapy, in the hippocampal cluster identified in a metaanalysis of PTSD neuroimaging studies<sup>20</sup> where PTSD patients were compared to trauma-exposed controls ( $F_{1,38} = 4.42$ ,  $p = 0.042$ ,  $\eta_p^2 = 0.10$ ), and the bilateral anatomic hippocampus defined using the AAL template ( $F_{1,38} = 7.07$ ,  $p = 0.011$ ,  $\eta_p^2 = 0.16$ ; Table 2 and Appendix 1, Fig. S1, available at [jpn.ca/190027-a1](http://jpn.ca/190027-a1)).<sup>43</sup>

We also conducted ROI analyses on clusters in the ventromedial prefrontal cortex and anterior cingulate cortex identified in the meta-analysis of PTSD neuroimaging studies mentioned above<sup>20</sup> and the bilateral anatomic amygdala defined using the AAL template.<sup>43</sup> However, we observed no significant results (Appendix 1, Table S1).

### Psychological questionnaire analyses

Repeated-measures analysis of variance revealed a main effect of time, with significant reductions in PTSD symptoms (PDS:  $F_{2,68} = 7.19$ ,  $p = 0.001$ ,  $\eta_p^2 = 0.17$ ) and trait anxiety (STAI Form X-2:  $F_{2,68} = 3.64$ ,  $p = 0.031$ ,  $\eta_p^2 = 0.09$ ), but no significant reductions in depression symptoms (BDI:  $F_{2,68} = 2.67$ ,  $p = 0.076$ ,  $\eta_p^2 = 0.07$ ). The group  $\times$  time interaction was not significant for the PDS ( $F_{2,68} = 0.27$ ,  $p = 0.76$ ,  $\eta_p^2 = 0.01$ ) or BDI ( $F_{2,68} = 0.27$ ,  $p = 0.765$ ,  $\eta_p^2 = 0.01$ ), but we did find a significant interaction for the STAI ( $F_{2,68} = 3.15$ ,  $p = 0.049$ ,  $\eta_p^2 = 0.08$ ). We then conducted post hoc paired-sample  $t$  tests to compare symptom levels pre-therapy to those at 6-month follow-up. Both groups continued to show a significant improvement in PTSD symptoms from pre-therapy levels at 6-month follow-up (PDS Tetris  $t_{17} = 1.93$ ,  $p = 0.036$ ; PDS control  $t_{17} = 3.39$ ,  $p = 0.002$ ; significance 1-tailed). Only the Tetris group continued to show a significant reduction in anxiety symptoms (STAI Tetris  $t_{17} = 1.93$ ,  $p = 0.035$ ; STAI control  $t_{17} = 0.57$ ,  $p = 0.29$ ; significance 2-tailed), but no significant reduction in depression symptoms (BDI Tetris  $t_{17} = 1.00$ ,  $p = 0.165$ ;

**Table 1: Demographic characteristics of study participants**

Characteristic	Tetris, mean $\pm$ SD	Therapy only, mean $\pm$ SD	$t$ test
Age, yr	34.2 $\pm$ 7.3	32.5 $\pm$ 5.3	$t_{38} = 0.79$ ; $p = 0.43$
Military deployment, d	354.9 $\pm$ 305.6	345.9 $\pm$ 214.2	$t_{38} = 0.11$ ; $p = 0.92$
CES score	32.2 $\pm$ 12.9	34.4 $\pm$ 16.7	$t_{38} = 0.60$ ; $p = 0.55$
EMDR sessions, $n$	7.0 $\pm$ 1.6	7.3 $\pm$ 1.9	$t_{38} = 0.62$ ; $p = 0.54$
Pre/post interval, d	39.9 $\pm$ 4.8	36.8 $\pm$ 6.6	$t_{38} = 1.74$ ; $p = 0.09$
Post/follow-up interval, d*	204.1 $\pm$ 57.4	256.4 $\pm$ 138.5	$t_{34} = 1.48$ ; $p = 0.15$

CES = Combat Experiences Scale; EMDR = eye movement desensitization and reprocessing; SD = standard deviation.

\*Follow-up data were missing for 4 participants (2 Tetris, 2 therapy-only controls).

BDI control  $t_{17} = 0.24$ ,  $p = 0.41$ ; significance 1-tailed) at 6-month follow-up (Fig. 2A).

To explore associations between neural and clinical change, we correlated changes in hippocampal volume with changes in psychological symptoms. Using the cluster identified in the whole-brain analysis, we found that increased hippocampal volume after therapy was correlated with further reduction of symptoms between completion of therapy and follow-up in the Tetris group, but not in the control group (Fig. 2B).

## Discussion

We found evidence that completing a visuospatial video-gaming intervention during psychological therapy for PTSD

led to increases in hippocampal volume and maintenance of a wider range of therapy-related gains, and increases in hippocampal volume correlated with further reductions in symptoms at 6-month follow-up. At the brain structural level, we found larger hippocampal volumes in the Tetris group in both the whole brain and the ROI analyses. At the psychological level, directly after therapy both groups showed reductions in PTSD, depression and anxiety symptoms. At 6-month follow-up, both groups continued to show reduced PTSD symptoms, but only the Tetris group continued to show reduced anxiety symptoms. In addition, hippocampal grey matter increases during therapy were correlated with further reductions in PTSD, depression and anxiety symptoms from discharge to follow-up in the Tetris group but not the control group.

**Table 2: Grey matter volume from whole-brain and ROI hippocampal neuroimaging analyses**

Variable	Group	Pre, mm <sup>3</sup> *	Post, mm <sup>3</sup> *	Time	Time × group	Group
Voxel-based morphometry hippocampus cluster	Tetris	0.43 ± 0.07	0.44 ± 0.07	$F_{1,38} = 9.04$ $p = 0.005$ § $\eta_p^2 = 0.19$	$F_{1,38} = 9.30$ $p = 0.004$ § $\eta_p^2 = 0.19$	$F_{1,38} = 0.167$ $p = 0.68$ $\eta_p^2 = 0.01$
	Therapy only	0.43 ± 0.03	0.43 ± 0.03			
Meta-analysis hippocampus†	Tetris	0.53 ± 0.05	0.54 ± 0.04	$F_{1,38} = 1.382$ $p = 0.25$ $\eta_p^2 = 0.03$	$F_{1,38} = 4.419$ $p = 0.042$ § $\eta_p^2 = 0.10$	$F_{1,38} = 0.008$ $p = 0.92$ $\eta_p^2 = 0.01$
	Therapy only	0.53 ± 0.03	0.53 ± 0.03			
Bilateral anatomic hippocampus‡	Therapy only	0.45 ± 0.04	0.45 ± 0.04	$F_{1,38} = 2.13$ $p = 0.15$ $\eta_p^2 = 0.05$	$F_{1,38} = 7.07$ $p = 0.011$ § $\eta_p^2 = 0.16$	$F_{1,38} = 0.006$ $p = 0.94$ $\eta_p^2 = 0.01$
	Tetris	0.45 ± 0.02	0.45 ± 0.02			

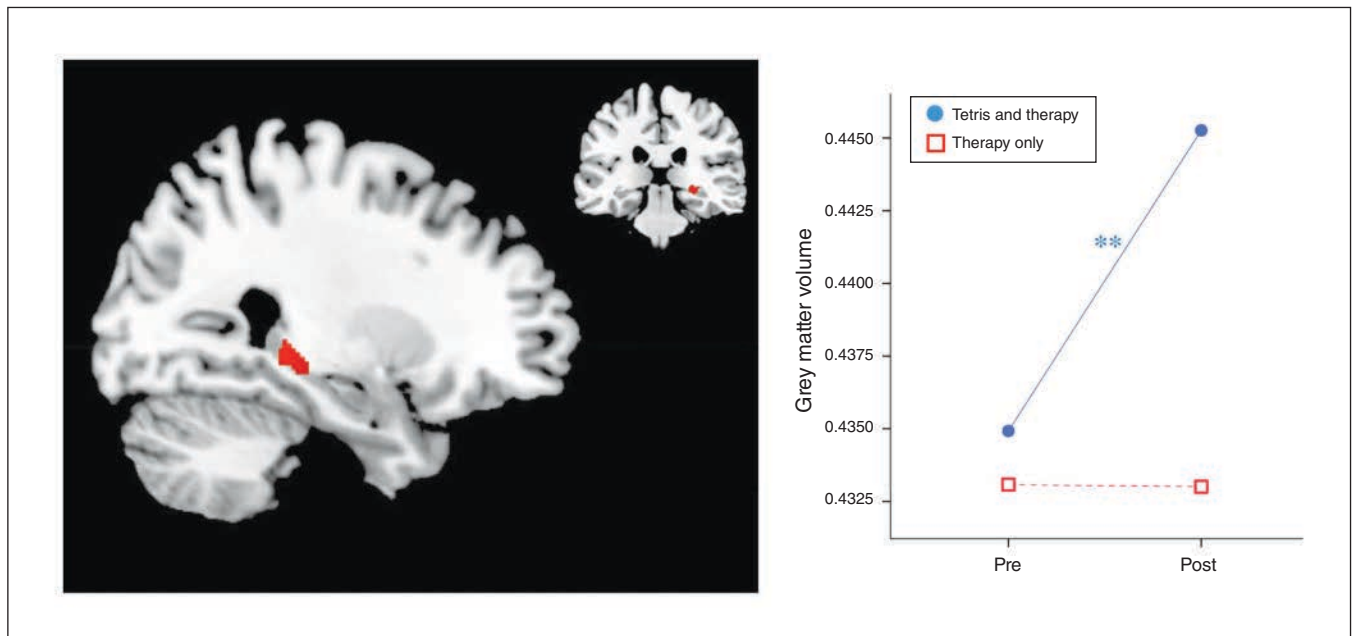
PTSD = posttraumatic stress disorder; ROI = region of interest.

\*Values are given as mean ± standard deviation.

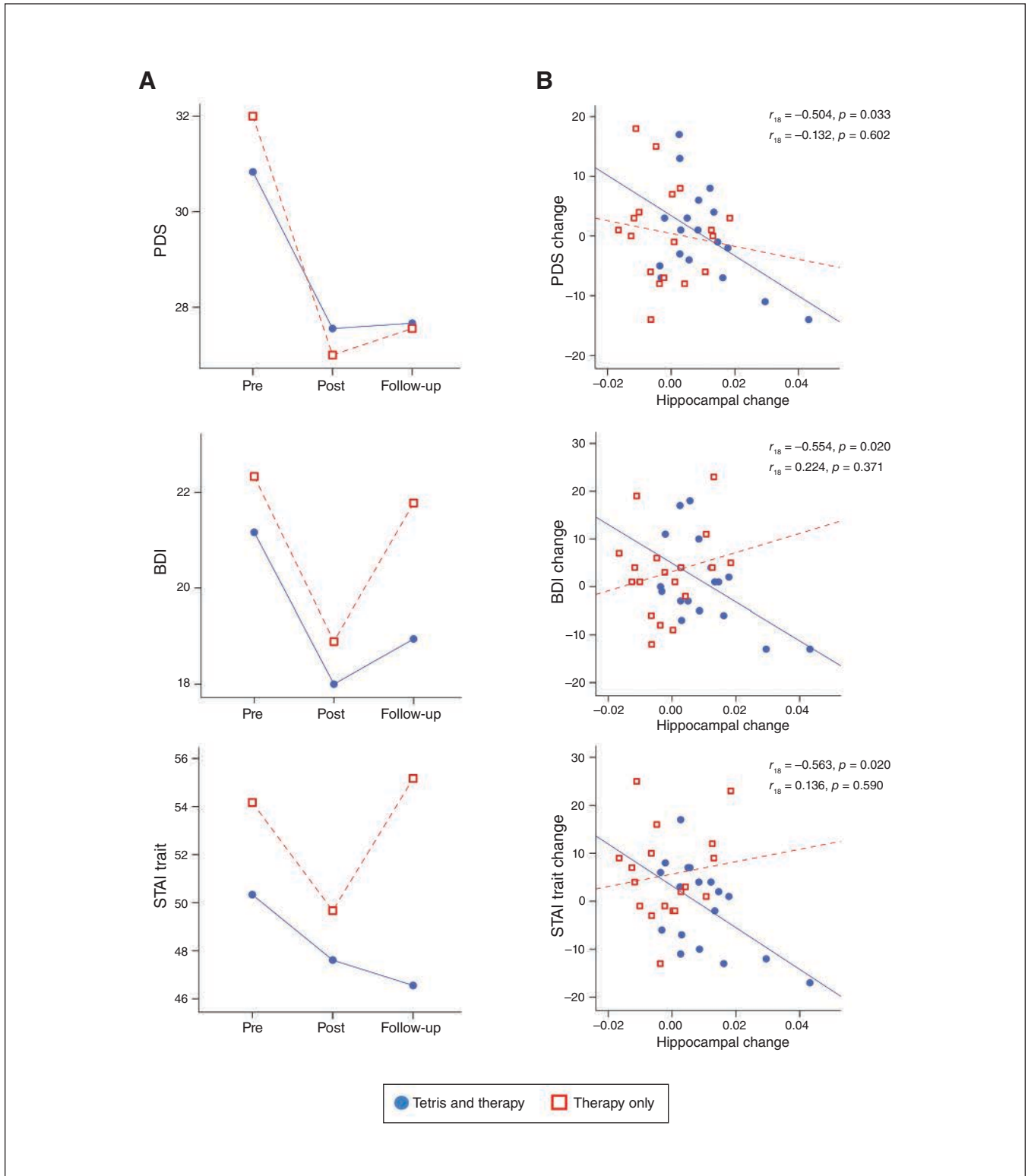
†Left anterior hippocampal cluster identified in a meta-analysis of PTSD neuroimaging studies.<sup>20</sup>

‡Bilateral anatomic hippocampus defined using the anatomic automatic labelling template.<sup>43</sup>

§Significant at  $p < 0.05$ .



**Fig. 1:** Neuroimaging results of whole-brain analysis. Brain image displays the cluster from a whole-brain analysis across all participants, comparing increases in the Tetris group to the therapy-only control group after treatment ( $k = 150$ ;  $x = 27$ ,  $y = -33$ ,  $z = -3$ ;  $p < 0.001$  at the voxel level, and  $k > 100$ , non-isotropic smoothness corrected at the cluster level). Post = directly after therapy; pre = before therapy.



**Fig. 2:** Psychological questionnaire scores and hippocampal grey matter. (A) Psychological questionnaire scores are displayed separately for the Tetrakis and therapy-only control groups, at 3 time points: before therapy (pre), directly after therapy (post) and approximately 6 months later (follow-up). (B) Increases in hippocampal volume after therapy were correlated with decreases in symptoms at follow-up in the Tetrakis group, but not in the therapy-only control group. Follow-up data were missing for 4 participants (2 Tetrakis, 2 therapy-only controls). Analyses based on 36 participants. BDI = Beck Depression Inventory; PDS = Post-traumatic Diagnostic Scale; STAI = State Trait Anxiety Inventory.

We observed a volume increase in the hippocampus but not in prefrontal regions such as the ventromedial prefrontal cortex and anterior cingulate cortex, in both the whole-brain and ROI analyses. The hippocampus is involved in memory, learning and fear extinction,<sup>44</sup> and the ventromedial prefrontal cortex and anterior cingulate cortex are involved in affective and cognitive processing and the regulation of fear expression.<sup>45</sup> Smaller hippocampal volumes have been associated with increased risk for PTSD<sup>25</sup> and with poorer prognosis;<sup>21–24</sup> smaller volumes in the prefrontal cortex may represent a more general effect of stress exposure.<sup>46,47</sup> At a structural level, the hippocampus is one of the most plastic regions in the human brain; it is rich in glucocorticoid receptors, making it highly susceptible to the effects of stress. In addition, reduction in glucocorticoid receptor function may lead to hyperactivity in the hypothalamus–pituitary–adrenal axis, leading to increased levels of glucocorticoids and further reductions in hippocampal volume.<sup>48</sup> Stress has been shown to produce dendritic atrophy and reductions in neurogenesis in the hippocampus,<sup>49</sup> and stress-induced alterations in the hippocampus have been linked to reductions in memory and cognition<sup>50</sup> and increases in anxiety-related behaviour.<sup>51</sup> Conversely, training studies have demonstrated that increases in hippocampal volume can be produced with a wide variety of interventions,<sup>29,30</sup> including video-gaming interventions.<sup>31</sup> The hippocampus is also involved in spatial orientation and navigation, and spatial learning has been linked to increases in hippocampal volume.<sup>52</sup> As such, sustained focus on a demanding visuospatial task such as Tetris may produce increases in hippocampal volume, driven in part by increases in neurogenesis. In animal models, hippocampal neurogenesis has been shown to mediate forgetting and support new learning.<sup>53</sup> Newly formed neurons compete with existing neurons for connections, and these newly formed connections may come to replace old ones, weakening existing memories and strengthening new ones.<sup>53</sup> Therefore, we propose that video-gaming-related increases in hippocampal neurogenesis may lead to subsequent reductions in PTSD symptoms by weakening memories of the traumatic event and strengthening memories formed during therapy.

Tetris provides a promising therapeutic intervention for a number of practical reasons. The video-gaming consoles required are inexpensive and mobile, and they can be reused multiple times. Tetris does not require a clinician to administer; it can even be self-administered. Tetris does not produce adverse effects and is enjoyable to play, so adherence is likely to be high. Tetris is also adaptive; as a person continues to play, the difficulty level (the speed at which the blocks fall) automatically increases until the game ends (the blocks fill the screen), at which point the game restarts at the lowest difficulty. As such, by adapting the level of difficulty to the skill of the player, it is possible to minimize frustration that the game is too difficult and boredom that the game is too easy, and the player should remain engaged in the game.

The current study builds on previous work using Tetris as the visuospatial task of choice.<sup>1–4</sup> However, other demanding visuospatial working-memory tasks, including other video games, could also be used successfully for PTSD. Attention

and engagement with a task is known to be a key factor in producing training-related gains at both the behavioural and neural levels.<sup>54</sup> Providing a range of games from which a person could choose could help maintain motivation and compliance, particularly for those outside of a clinical setting.

In the current study, we assessed combat-exposed young adult males. It is possible that trauma type, age, sex and military status could mediate the effect of a video-gaming intervention on the brain. Sex and age have been shown to play a role in resilience to stress<sup>49</sup> and hippocampal neuroplasticity,<sup>55</sup> as well, military and civilian PTSD populations have been shown to differ in risk factors<sup>56</sup> and response to psychotherapy.<sup>11</sup> Future work may seek to explore the utility of video game interventions for female and civilian PTSD populations.

### Limitations

At the time of study initiation, no study had attempted to use Tetris as an intervention to target memory reconsolidation or for people with current PTSD. We considered Tetris to be a promising adjunct to EMDR therapy, both as a cognitive interference task targeting reconsolidation of traumatic memories after reactivation during therapy, and as a brain-training intervention targeting the hippocampus. We consider the current results to be an initial proof of concept of the utility of Tetris as an adjunct therapeutic intervention. However, with the current design it was not possible to distinguish the cognitive-interference elements of the Tetris intervention from the brain-training elements. In addition, given the novel nature of this work, we used a standard-of-care control group. A standard-of-care control group is a widely accepted approach for assessing the effectiveness of a novel therapeutic intervention in conditions with existing therapeutic interventions. Future work may seek to employ a game active control group to test whether the observed effects were specific for Tetris and to distinguish potential brain-training effects from cognitive-interference effects. In addition, patients with PTSD may show signs of cognitive impairment,<sup>57</sup> and increases in hippocampal volume have been linked to increases in cognitive performance after therapy for PTSD.<sup>28</sup> Future work may seek to explore if Tetris-related changes in hippocampal volume are associated with improvements in cognitive performance in patients with PTSD.

It should be noted that more conservative approaches could be adopted for the neuroimaging analyses. However, the current sample size was small, because of the non-trivial challenge of recruiting this patient population. As such, we sought to balance concerns of type I and type II errors in our analysis by applying the less conservative approach of a voxel-level threshold of  $p < 0.005$  combined with cluster-size correction, a method that is accepted and published.<sup>47,58</sup>

Conversely, we also note that we did not observe effects in the prefrontal cortex, despite the fact that these regions are reduced in PTSD populations<sup>18–20</sup> and have been shown to respond to video-gaming interventions.<sup>31</sup> The timeline of changes in the hippocampus and prefrontal cortex may differ, with the prefrontal cortex showing an initial period of

expansion followed by a period of renormalization.<sup>59</sup> Future studies may seek to use multiple neuroimaging assessments over the course of therapy to assess the rate and pattern of neural changes. Alternatively, due to the small sample size the current study may simply have been underpowered to detect changes in the prefrontal cortex.

At the behavioural level, we observed an interesting trend toward reductions in depression symptoms at 6-month follow-up in the Tetris group, although this finding was not statistically significant. As previously noted, we consider the current results to be an initial proof of concept. However, future work with larger sample sizes is needed further to explore the utility of Tetris as an adjunct therapeutic intervention and the underlying neural mechanisms.

## Conclusion

Current interventions for PTSD have a number of limitations with respect to response rates and long-term efficacy, and there is a significant need for additional therapeutic interventions that can act as an adjunct to traditional psychotherapy. We provide evidence that Tetris may be useful as an intervention for people with current PTSD, alongside EMDR psychotherapy. After completion of psychotherapy, symptoms were reduced across all participants, and both groups continued to show reductions in PTSD symptoms at 6-month follow-up. However, only the Tetris group continued to show reductions in anxiety symptoms and a trend toward reductions in depression symptoms at 6-month follow-up. Playing Tetris was correlated with increases in hippocampal volume, and hippocampal increases were correlated with continued reduction of PTSD, depression and anxiety symptoms between completion of therapy and 6-month follow-up. As such, Tetris playing may ensure that a wider range of symptom improvements are maintained after therapy, through increases in hippocampal volume.

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**Data sharing:** Key data and materials have been made publicly available via the Open Science Framework and can be accessed at [osf.io/xz32u](https://osf.io/xz32u), or are otherwise available from the authors on request (with the exception of questionnaire measures subject to third-party copyright or potentially identifying patient information).

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