

LETTER TO THE EDITOR

Post-retrieval Tetris should not be likened to a ‘cognitive vaccine’

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Iyadurai *et al.*¹ report a randomized controlled trial intended to mitigate post-trauma symptoms in motor vehicle collision (MVC) survivors presenting to an emergency department. The intervention, motivated by memory ‘(re)consolidation’ theory, consisted of a brief reminder of the accident followed by playing the computer game Tetris. The findings are taken to indicate a promising preventive intervention akin to a ‘cognitive therapeutic vaccine’ and comparable to ‘a rabies vaccine after a dog bite’ (p. 7). We will describe several reasons why this characterization is misleading.

The trial aims to reduce memory intrusions as a relevant clinical outcome *per se*, but also as a surrogate end point, whereby intrusions would represent a risk factor for subsequently developing other mental disorders, primarily post-traumatic stress disorder (PTSD). It is imperative these objectives are not conflated, as the trial does not support any compelling inferences about PTSD. First, Iyadurai *et al.* imply that memory intrusions are predictive of subsequent PTSD development, but the cited evidence is weak and inconclusive. One study² actually showed that post-trauma intrusions had a small predictive effect on PTSD development, not statistically significant when analyses were adjusted for other relevant predictors. The extension of the other study cited, a machine learning application, did not find a predictive role for early re-experiencing.³ Second, the ‘anxious-re-experiencing’ type of PTSD accounts for about 32% of diagnosed patients, but is mostly associated with interpersonal violence and has only a weak relationship with MVC.⁴ Third, a longer follow-up would have been needed to accurately assess PTSD development, which requires at least 1 month containing a minimum of 6 out of 20 possible symptoms,⁵ intrusions being just one type.

Even if the conclusions of the trial were limited to memory intrusions as a clinically relevant end point *per se*, the findings can hardly be construed as equivalent to an effective ‘vaccination’. Interpretation of the trial focuses on the effect of post-retrieval Tetris on the total number of ‘intrusive memories’ recorded in a daily diary after 1 week ($d=0.67$). The authors suggest that the intervention ‘could substantially improve the mental health of those who have experienced psychological trauma’ (p. 7). However, the benefits of Tetris may be overstated: visual inspection of the per-protocol data (made available by the authors at <https://osf.io/e4hc7/>) suggests that the magnitude of the effect may be heavily influenced by non-normality and extreme values in the control group who recorded a high number of intrusions (Figure 1a). An exploratory sensitivity analysis using medians as a more robust indicator of central tendency indicated that the effect is far weaker (Figure 1a), though still statistically significant with the non-parametric Wilcoxon test ($P=0.02$).

Furthermore, although the diary measure was used in the authors’ own preclinical work, no systematic assessment of its reliability or validity has been reported. By contrast, the Impact of Event Scale-Revised (IES-R), though only considered as a secondary outcome, includes a dedicated intrusions subscale, and has extensive reliability and validity data, even specifically for the target population: MVC survivors.⁶ Accordingly, it is important to emphasize that 1-week IES-R intrusion effects were also small (Figure 1b) and, critically, no effect of the intervention was observed at 1 month for this measure, or for any other symptom outcomes (Figure 1c). The authors fully attribute this to insufficient statistical power. Nonetheless, another possibility is that the 1 week effects were small and transient.

Finally, the trial is presented as a ‘compelling translation of previous laboratory findings’ (p. 7). In the Introduction and in these previous laboratory studies the authors cite foundational studies in the fields of consolidation and reconsolidation. The trial

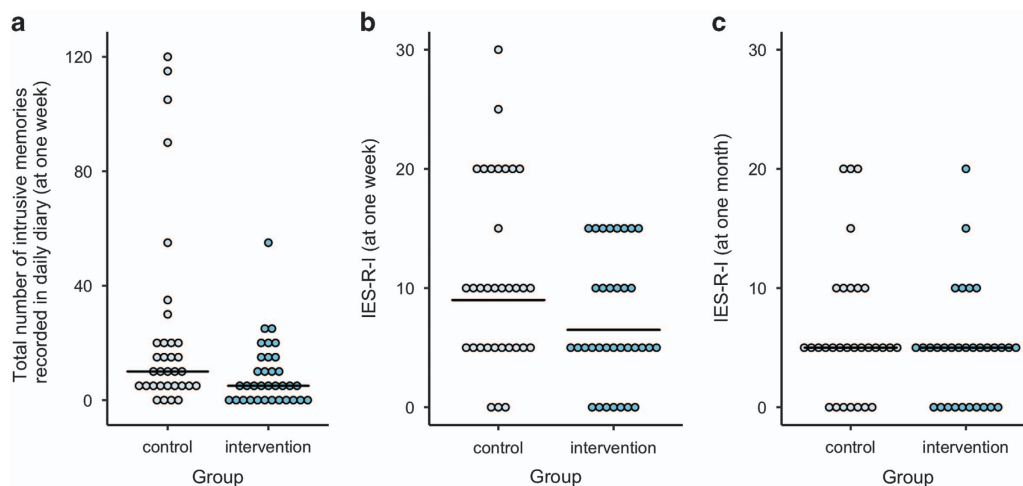


Figure 1. Intrusion measures as a function of group (control and intervention). Dots show individual data points (bins = 5), horizontal black bars show medians (Md). (a) Total number of intrusive memories recorded in the diary over 1 week: control (Md = 10) and intervention (Md = 5). (b) Impact of Event Scale-Revised intrusion subscale (IES-R-I) at 1 week: control (Md = 9) and intervention (Md = 6.5). (c) IES-R-I at 1 month: control (Md = 5) and intervention (Md = 5).

seems to have combined procedural elements stemming from both memory consolidation (an intervention window under 6 h) and reconsolidation (use of a reminder cue).

It is pertinent to note that the validity of both concepts has been strongly contested, both theoretically⁷ and empirically.⁸ Evidence for (re)consolidation is traditionally derived from non-human animal studies using highly invasive interventions that target the putative molecular substrates of the stabilization process. Evidence for reconsolidation in humans based on pharmacological interventions is accruing, but outcomes remain highly mixed.⁹ The rationale for expecting a behavioural intervention to influence the reconsolidation process is also far from clear.⁸ Human reconsolidation studies that rely on post-retrieval behavioural interventions (as used in this trial) are especially controversial, with many initially promising results^{10,11} proving elusive in subsequent replication attempts.^{8,12} This is not the firm theoretical or empirical foundation implied in the article.

While this trial does not justify comparing post-retrieval Tetris to a 'therapeutic vaccine', future research could clarify its preventive effectiveness for intrusions or PTSD. This does not simply entail larger trials, but also heeding to the several limitations identified here. A heterogeneous sample should be recruited, including not just MVC survivors, but also victims of interpersonal violence, for whom intrusions are more frequent. Participants could be pre-screened for high levels of intrusions, as these will not be equally prognostic for all trauma victims. Primary outcomes need to be assessed with reliable validated symptom scales, and must include PTSD symptoms, so that the full effects of the intervention are assessed. Finally, participants need to be followed long enough (8 weeks) so as to evaluate PTSD onset, with both self-report and clinician-based instruments. Conducting such a trial would be costly and difficult, so the judiciousness of the investment should be weighed against the risk of it producing null findings and not meaningfully informing treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Data availability statement: Data and analysis scripts are publicly available on the Open Science Framework (<https://osf.io/2mcra/>).

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REFERENCES

- 1 Iyadurai L, Blackwell SE, Meiser-Stedman R, Watson PC, Bonsall MB, Geddes JR *et al.* Preventing intrusive memories after trauma via a brief intervention involving Tetris computer game play in the emergency department: a proof-of-concept randomized controlled trial. *Mol Psychiatry* 2017; e-pub ahead of print 28 March 2017; doi: <https://doi.org/10.1038/mp.2017.23>.
- 2 Creamer M, O'Donnell ML, Pattison P. The relationship between acute stress disorder and posttraumatic stress disorder in severely injured trauma survivors. *Behav Res Ther* 2004; **42**: 315–328.
- 3 Karstoft KI, Galatzer-Levy IR, Statnikov A, Li Z, Shalev AY. Bridging a translational gap: using machine learning to improve the prediction of PTSD. *BMC Psychiatry* 2015; **15**: 30.
- 4 Pietrzak RH, el-Gabalawy R, Tsai J, Sareen J, Neumeister A, Southwick SM. Typologies of posttraumatic stress disorder in the U.S. adult population. *J Affect Disord* 2014; **162**: 102–106.
- 5 Association AP. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. American Psychiatric Association: Arlington, VA, USA, 2013.
- 6 Beck JG, Grant DM, Read JP, Clapp JD, Coffey SF, Miller LM *et al.* The impact of event scale-revised: psychometric properties in a sample of motor vehicle accident survivors. *J Anxiety Disord* 2008; **22**: 187–198.
- 7 Millin PM, Moody EW, Riccio DC. Interpretations of retrograde amnesia: old problems redux. *Nat Rev Neurosci* 2001; **2**: 68–70.
- 8 Hardwicke TE, Taqi M, Shanks DR. Postretrieval new learning does not reliably induce human memory updating via reconsolidation. *Proc Natl Acad Sci USA* 2016; **113**: 5206–5211.
- 9 Beckers T, Kindt M. Memory reconsolidation interference as an emerging treatment for emotional disorders: strengths, limitations, challenges, and opportunities. *Ann Rev Clin Psychol* 2017; **13**: 99–121.
- 10 Schiller D, Monfils MH, Raio CM, Johnson DC, Ledoux JE, Phelps EA. Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature* 2010; **463**: 49–53.
- 11 Walker MP, Brakefield T, Hobson JA, Stickgold R. Dissociable stages of human memory consolidation and reconsolidation. *Nature* 2003; **425**: 616–620.
- 12 Kindt M, Soeter M. Reconsolidation in a human fear conditioning study: a test of extinction as updating mechanism. *Biol Psychol* 2013; **92**: 43–50.