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

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Iyadurai and colleagues[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 endpoint, 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. Firstly, Iyadurai et al. imply that memory intrusions are predictive of subsequent PTSD development, but the cited evidence is weak and inconclusive. One study[2] 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]. Secondly, 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]. Thirdly, 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 endpoint *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 one week (d = .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 raw data[i] 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 employing medians as a more robust indicator of central tendency indicated that the effect is far weaker (see Figure 1), though still statistically significant with the non-parametric Wilcoxon test (p = .02).

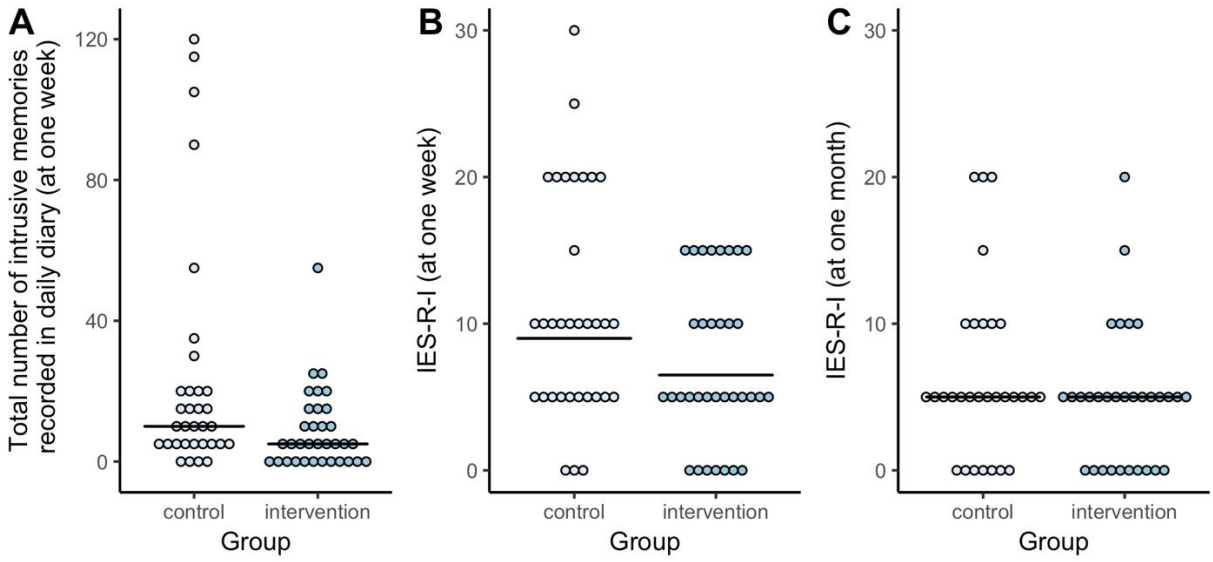

Figure 1. Intrusion measures as a function of group (control, intervention). Dots show individual data points (bins = 5), horizontal black bars show medians (*Md*). **A**: Total number of intrusive memories recorded in the diary over one week: control (*Md* = 10) and intervention (*Md* = 5). **B**: Impact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

[i] Analyses only pertain to the per-protocol data made available by the authors at https://osf.io/e4hc7/.

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

It is pertinent to note that the validity of both concepts has been strongly contested, both theoretically[7] 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 employed 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 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.

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