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Processing confusing procedures in the recent re-analysis of a cognitive bias modification meta-analysis

Those worried about the cognitive bias modification (CBM) field being affected by ever-moving goal posts may have thought their concerns confirmed by Grafton and colleagues' re-analysis of the meta-analysis by Cristea and colleagues.[1,2] The paper concludes with the suggestion that we should only call CBM CBM if it is successful. To provide a treatment-inspired analogue: 'This? No, this is just water, it's only homoeopathy if it works'.

It seems that we witness an almost prototypical disagreement between experimentalists and treatment evaluationists about which question to ask and which data to include. Importantly, the two author groups appear quite agreed that the answer to the question 'whether assigning an anxious individual to engage in a CBM procedure will result in direct symptom reduction' would be 'not likely'. Perhaps Grafton and colleagues had better direct their critical attention towards the work by 'field insiders' in which CBM is quite consistently touted as a treatment, not to mention the apparent push for clinical dissemination and premature commercial exploitation. Thus, the question meta-analysed by Cristea and colleagues, authors specialising in meta-analytical evaluation of (proposed) treatments, appears perfectly legitimate.

Grafton and colleagues' exposé on the correct question to meta-analyse, reads uncomfortably like a perceived-damage-containing mission. The discomfort is aggravated by the presented re-analysis, applying dichotomising and partly mystifying criteria to distil a subset of eligible studies from those selected for the original meta-analysis. Specifically, the requirements for a study to pass 'Criterion 3: effect size computed by Cristea *et al* reflects legitimate emotional vulnerability assessment' (Table 1, p. 268) remain unknown, as do the rules governing the final dividing criterion 'intended CBM procedure successfully induced the process of bias modification' (p. 268).

One could attempt to reconstruct the criterion rules from the tables provided, but it matters little. The analysis by Grafton and colleagues is flawed in a manner that must have escaped the attention of authors, reviewers and editors alike, even after Cristea and colleagues pointed it out in their commentary.[3] To be very explicit: Grafton *et al* meta-analysed the study effect-size estimates calculated by Cristea *et al*.

In their original paper,[1] Cristea and colleagues state clearly that (a) for studies reporting multiple symptom outcomes, these were averaged into a single effect-size estimate (p. 8), and (b) effect-size estimates reflect symptoms assessed post-training, excluding assessments following a stressor procedure (p. 9).

Based on the narrative, it appears that criterion 3 has to do with each study either (a) assessing symptoms on trait (rather than state) measures, yet effect-size estimates averaging across state and trait measures were analysed, or (b) employing a post-training stressor procedure, yet symptoms assessed preceding such stressor procedures were analysed. Surely, we are not to assume reliable retro-active impact of unannounced stressors, nor that excluding studies with state measures only, results in adjustment of state measures retained for other studies. Therefore, we must conclude that this small yet crucial detail has gone unnoticed.

A meta-analysis by Grafton and colleagues, assessing evidence for their hypotheses, could perfectly exist alongside the meta-analysis by Cristea and colleagues. The currently presented re-analysis, however, does not convince.

1 Cristea IA, Kok RN, Cuijpers P. Efficacy of cognitive bias modification interventions in anxiety and depression: meta-analysis. *Br J Psychiatry* 2015; **206**: 7–16.

2 Grafton B, MacLeod C, Rudaizky D, Holmes EA, Salemink E, Fox E, et al. Confusing procedures with process when appraising the impact of cognitive bias modification on emotional vulnerability. *Br J Psychiatry* 2017; **211**: 266–71.

3 Cristea IA, Kok RN, Cuijpers P. Invited commentary on … Confusing procedures with process in cognitive bias modification research. *Br J Psychiatry* 2017; **211**: 272–3.

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Authors' reply: Kruijt & Carlbring misrepresent the position conveyed in our commentary,[1] wrongly attributing to us the suggestion 'that we should only call CBM CBM if it is successful'. Our actual points are: (a) it cannot be claimed that cognitive bias has been modified when assessment data reveal that no modification of cognitive bias has taken place; and (b) the emotional impact of modifying cognitive bias cannot be determined from studies that fail to modify cognitive bias. Also, incorrectly, they describe our commentary as an 'exposé on the correct question to meta-analyse'. We highlight the need to distinguish two quite different questions, without claiming that either is 'correct', and emphasise the resulting problems when meta-analyses fail to do so.

Our position adheres to the tenets of experimental medicine.[2] The first step in experimental medicine is to identify a target *mechanism* that plausibly contributes to the *dysfunction* of interest. For example, high blood pressure represents a *mechanism* that may contribute to the *dysfunction* of elevated stroke risk, and attentional bias to threat represents a *mechanism* that may contribute to the *dysfunction* of anxious disposition. Step two involves developing a candidate *intervention* intended to manipulate this *mechanism*. This could involve a drug intended to reduce blood pressure, or a computer procedure intended to reduce attentional bias to threat. Step three involves delivering the *intervention* to determine: (a) whether the *intervention* impacts the *mechanism*, as intended; and if so (b) whether this impact on *mechanism* therapeutically attenuates *dysfunction*. Should the drug fail to reduce blood pressure, with no observed reduction in stroke risk, it cannot be concluded that reducing blood pressure has no impact on stroke risk. Likewise, should the computer procedure fail to modify attentional bias to threat, with no observed reduction in anxious disposition, it cannot be concluded that modifying attentional bias to threat has no impact on anxious disposition. If the drug sometimes reduces blood pressure, and whenever this occurs stroke risk also decreases, this suggests that blood pressure reduction attenuates stroke risk. Likewise, if the computer procedure sometimes reduces attentional bias to threat, and whenever this occurs anxious disposition also decreases, this suggests that attentional bias modification alters anxious disposition.

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We re-analysed Cristea *et al*'s[3] effect sizes to demonstrate that, when procedures intended to modify cognitive bias elicit the process of cognitive bias modification, there is consistent impact on emotional disposition. Kruijt & Carlbring contend that Cristea *et al*'s method of computing effect sizes compromises sensitivity to emotional disposition, which would represent a further limitation of this meta-analysis. However, compelling evidence that when procedures intended to evoke the process of cognitive bias modification do so successfully then so too do they alter emotional disposition, is not restricted to our re-analysis, and has been reported elsewhere.[4]

We advocate adherence to the experimental medicine framework, by clearly distinguishing two questions: one asks whether successfully modifying cognitive bias yields therapeutic benefit, and the other asks whether procedures intended to modify cognitive bias successfully induce this process of cognitive change.

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1 Grafton B, MacLeod C, Rudaizky D, Holmes EA, Salemink E, Fox E, et al. Confusing procedures with process when appraising the impact of cognitive bias modification on emotional vulnerability. *Br J Psychiatry* 2017; **211**: 266–71.

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3 Cristea IA, Kok RN, Cuijpers P. Efficacy of cognitive bias modification interventions in anxiety and depression: meta-analysis. *Br J Psychiatry* 2015; **206**: 7–16.

4 Price RB, Wallace M, Kuckertz JM, Amir N, Graur S, Cummings L, et al. Pooled patient-level meta-analysis of children and adults completing a computer-based anxiety intervention targeting attentional bias. *Clin Psychol Rev* 2016; **50**: 37–49.

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Author's reply: Kruijt & Carlbring judiciously uncover significant methodological problems of the narrative re-analysis by Grafton and colleagues[1] on our previous meta-analysis on the effectiveness of cognitive bias modification (CBM) interventions in anxiety and depression.[2] The letter reinforces what we had previously noted in our invited comment,[3] namely that our approach had been grossly misconstrued. In the meta-analysis, we had pooled *all* anxiety outcomes measured on validated instruments at post-intervention, whether these measured clinical symptoms, state or trait anxiety. We specifically excluded measures applied after a stressor induction task. If multiple measures in the same outcome category (for example general anxiety) were reported, we averaged them at study level. Grafton and colleagues claim to have re-analysed the anxiety data so as to reflect 'change in emotional vulnerability' (p. 268). Not only is this construct vague and its application susceptible to bias, but, as Kruijt & Carlbring justly note, Grafton *et al* simply selected some of the already computed effect sizes and pooled them again. Essentially, this approach reflects the same mix comprising all anxiety outcomes, measured in the absence of a stressor induction task, and averaged at study level, just stemming from a more restricted pool of studies. To implement their new set of criteria, Grafton and colleagues should have recalculated effect sizes from study-level data, excluding measures and time points they did not deem appropriate for the elusive construct of emotional vulnerability. As it is, their re-analysis remains an arbitrary *post hoc* selection of study effects.

Yet a larger and more crucial problem relies in the central claim of Grafton *et al*, echoed by many leading CBM advocates: the effectiveness of these interventions should only be weighed *if* they successfully modified bias. Kruijt & Carlbring adeptly liken this to familiar arguments for homeopathy. However, it also reflects a fundamental misunderstanding of how causal inferences and confounding function in a randomised design. Identifying the trials in which both bias and outcomes were successfully changed is only possible *post hoc*, as these are both outcomes measured after randomisation; reverse engineering the connection between the two is subject to confounding. Bias and symptom outcomes are usually measured at the same time points in the trial, thus making it impossible to establish temporal precedence.[4] Circularity of effects, reverse causality (i.e. bias change causes symptom change or vice versa) and the distinct possibility of third variable effects (i.e. another variable causing both symptom and bias changes) further confound this relationship.[4] For instance, trials where both bias and symptom outcomes were successfully modified could also be the ones with higher risk of bias, conducted by allegiant investigators, maximising demand characteristics or different in other, not immediately obvious, ways from trials where neither bias nor symptoms changed. Randomised controlled studies can only show whether an intervention to which participants were randomised has any effects on outcomes measured post-randomisation.[5] Disentangling the precise components causally responsible for such effects is speculative and subject to confounding. To this point, randomised studies show CBM has a minute, unstable and mostly inexistent impact of any clinically relevant outcomes.

1 Grafton B, MacLeod C, Rudaizky D, Holmes EA, Salemink E, Fox E, et al. Confusing procedures with process when appraising the impact of cognitive bias modification on emotional vulnerability *Br J Psychiatry* 2017; **211**: 266–71.

2 Cristea IA, Kok RN, Cuijpers P. Efficacy of cognitive bias modification interventions in anxiety and depression: meta-analysis. *Br J Psychiatry* 2015; **206**: 7–16.

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Towards a definition of unbearable suffering and the incongruence of psychiatric euthanasia

In the article by Verhofstadt *et al*, the authors rightly observe that the concept of 'unbearable suffering' in relation to euthanasia remains poorly defined in the medical literature.[1] We wish to make three observations which may contribute to a better understanding of 'unbearable suffering' and highlight the incongruence of considering euthanasia as psychotherapeutic.