PCN Psychiatry and Clinical Neurosciences

LETTER TO THE EDITOR

Response to: Examining the therapeutic potential and risks of multivoxel neuroreinforcement for specific phobias

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We thank Sithara *et al*. for highlighting a number of potential problems of our recent study[1] in a letter to the editor.[2] Here we address the concerns.

The authors wrote that for both our findings of reduced amygdala activity in our fear test task and reaction times in the affective Stroop task for the targeted phobia of neuroreinforcement "the maximum reduction … occurred in the outliers". However, for both of these effects, all data points fall within 3 standard deviations of the mean. For the reduction in amygdala response (Fig. 4a), the maximum reduction is at 2.24 SD, and removal of it does not change the fact that there is still a significant interaction between phobia type (target/control) and time (pre/post) shown by a 2 (condition) × 2 (time) repeated-measures ANOVA ($F_{(1,14)} = 5.25$, $P = 0.038$, $\eta_p^2 = 0.273$). For the affective Stroop task (Fig. 4b), the maximal reduction in reaction time is within 2.55 SD, and removal of it, again, leaves the overall pattern of results unchanged. We are thus unsure about the basis of the concern.

The authors also raised that "1/3 of participants had worsening amygdala responses or an increase in physiological fear". But these participants do not have significant worsening. Variability is expected in any group study, and the participants showing an increase are in the minority. This is why we used statistics to establish that overall, there is a significant decrease (i.e. improvement) in amygdala response as a group, which is standard for assessing the effectiveness of treatments.

It would be fruitful for future studies with sufficient between-subject power to explore factors that might increase or decrease the benefit of decoded neurofeedback. We recommend this for future endeavors.

Relatedly, the authors raised concerns that in supplemental fig. S3, there seems to be a "paradoxical increase" of amygdala responses in the 5-day group. As we note in the discussion of our paper, it is difficult to draw meaningful differences in these groups owing to the smaller-than-planned sample size. Additionally, the interaction of dosage group with amygdala response was not significant (as reported in Supplemental Results), indicating no statistically evident differences between groups for reduction in amygdala response.

In plots (S3b) and (S3c) - corresponding to the 3-day group and 5-day group in isolation, respectively - the standard errors of the mean overlap with 0. It should be noted that our previous proof-of-concept study showed robust effects using a 3-day dose for all participants.[3] There is thus perhaps little reason to worry that an increased dosage of neuroreinforcement would be harmful. We agree that future studies with higher statistical power need to be conducted to examine how responses change as a function of the duration of the intervention.

The letter authors also raise concerns that pre and post neuroreinforcement assessments were equally spaced for all dosage groups, rather than performing the post neuroreinforcement assessment immediately after the intervention. However, if we conducted the post assessment immediately after the final neuroreinforcement session and observed increased effects for each dosage group as we predicted, it would be impossible to discern whether this was due to the increased dosage of neuroreinforcement or the simple passage of time.

Relatedly, the letter authors raise the possibility that participants "may have encountered their phobic stimuli in real world settings". Participants were explicitly interviewed about their propensity to avoid these animals should they encounter them during the initial diagnostic interview. Sufficient avoidance is a criterion for inclusion in this study. Additionally, this incidental "exposure" would be quite different from the structured exposures of exposure therapy should any have happened.

Finally, given that our results primarily demonstrated a lessening of amygdala responses while subjective fear levels remained unchanged, this would suggest the observed results reflect an effect of our intervention, as this somewhat counterintuitive pattern matches previous results.[3] If these were attributable to exposure outside of our intervention, a corresponding lessening of subjective fear ratings would be expected - as in traditional *in vivo* exposure. The authors' concern is valid however and future studies would do well to more explicitly monitor for any incidental or purposeful exposure.

The letter authors also raised concerns about participants' potential prior experience with exposure therapy or treatment. There were multiple points during the clinical interview process where previous treatment would have become apparent. Firstly, during the diagnostic interview, participants were asked if they had ever encountered the potential phobic animal, and to provide the context of the encounter(s). No participant reported receiving exposure therapy in response to this question. Furthermore, participants were asked if they would seek treatment for their phobia, and no participants reported prior treatment in response, despite their being interested in treatment. Additionally, as this was ultimately a within-subjects design, participants' baseline fear responses and neurophysiological profiles were accounted for in our statistical analyses.

The letter authors also mention that it is not clear when exactly participants received their monetary bonus. Participants were fully aware of how much monetary reward they were accruing. Their average run scores were presented to them at the end of each run. The actual disbursement of cash occurred after the post-test in one sum total along with their payment for the study as a whole.

In conclusion, Sithara *et al*. raise a number of interesting potential concerns in their letter regarding our study. We thank them for this useful discussion. Hopefully, our responses here have addressed the issues. We are in agreement with the letter authors that future studies will be needed to better examine potential between-group differences in dosage effects for neuroreinforcement. Additionally, future studies can more explicitly question participants on previous attempted treatments for Specific Phobia as well as more accurately monitor for incidental exposure to phobic animals over the course of the study.

Disclosure statement

M.K. is an inventor of patents owned by the Advanced Telecommunications Research Institute International related to the present work (PCT/JP2012/078136 [WO2013/068719517] and PCT/JP2014/61543 [WO2014/178322]). C.A.C., H.L., M.G.C., and V.T-D. have no conflicts to declare.

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