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# Amygdala where art thou?

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The commentary of Morriss et al. on our recent meta-analysis of functional magnetic resonance imaging (fMRI) fear/threat extinction studies in humans (Fullana et al., 2018) raises some important issues for future research in the field. In essence, they argue that the lack of consistent evidence for amygdala and ventromedial prefrontal cortex (vmPFC) involvement in these studies, as summarized by meta-analysis, might be partly due to the fact that very few of these studies have provided appropriate analyses of time-varying neural responses, which Morriss et al. contend should be the gold standard.

Fear/threat conditioning and extinction learning are indeed incremental processes that develop on a trial-by-trial level (Rescorla and Wagner, 1972), and thus including trial factors in fMRI analyses of these processes may conceivably improve their characterization. However, we would like to reiterate our position on a couple of issues,

which we believe may more fundamentally influence the characterization of these regions in fMRI studies of conditioning and extinction processes.

First, the analysis of participant responses in fMRI threat/fear learning studies typically indicate states of mild anticipatory anxiety, and relief thereof, when contrasting CS+ and CS-, respectively. In addition, we can assume that participants are fully aware that their involvement in these experiments is safe, and that no genuine threat exists to their well-being. Thus, a more compelling explanation of the absence of amygdala involvement across fMRI fear/threat learning experiments might be that these experiments themselves are not strong probes of amygdala defense-survival circuit function. In other words, regardless of the application of time-varying analyses of amygdala responses, coupled with higher resolution imaging etc., these experiments may not be capable of eliciting the types or magnitudes of threat that have been shown to routinely elicit defense-survival responses in animal studies. By way of illustration, the results of our former meta-analysis of fMRI fear/threat conditioning studies (Fullana et al., 2016) lead one anonymous reviewer to remark: "the authors would do the community a great favor if they finally put away with the amygdalo-centric view on human fear conditioning (that is more based on rodent data than on any actual data from humans) and emphasized the role of other, mainly cortical, structures that are observed much more consistently". Accordingly, we feel that whilst innovations in modelling neural dynamics in fMRI fear/threat learning studies will be important in the future progress of this work, we should also confront the idea that these experiments may be fundamentally limited in the study of neural defense-survival circuits and may be better suited to addressing other aspects of the experience of threat/fear/anxiety and related mental states (see Fullana et al., 2016).

Second, the absence of consistent vmPFC involvement in the fear/threat extinction learning meta-analysis may originate in the test comparisons used to detect neural correlates of extinction in humans. As we have discussed at length in other work (Fullana et al., 2016; Harrison et al., 2017), vmPFC activation is reliably observed when the conditioning of safety (CS-) is compared to the conditioning of threat (CS+), and this differential response generalizes well across fear/threat learning states and contexts. But in extinction learning studies, the characterization of vmPFC responses has likely been confounded by choice of comparison (baseline) condition. For example, in all studies included in our meta-analysis, the primary fear extinction learning contrast was based on the comparison of responses to extinction CS+ ('now safe') vs. CS- ('still safe') stimuli. Using the latter as a 'baseline' condition is problematic, because any vmPFC activation to the 'now safe' signal (extinction CS+) will be largely subtracted out against continued vmPFC activation to the 'still safe' signal (extinction CS-). Indeed, our meta-analysis of extinction *recall* studies demonstrated reliable vmPFC activation in studies that compared extinguished CS+ to unextinguished ('still dangerous') CS+, but not in studies that compared extinguished CS+ to 'still safe' CS-.

In summary, we agree with Morris et al. that analyzing the trial factor is an important goal for future studies on fear and extinction learning, but we also highlight the challenges of (1) probing the survival-defensive circuit within the safety boundaries of human threat/fear learning experiments, and (2) identifying neutral baseline comparisons that are not contaminated by safety during extinction learning. Possible solutions lie in the use of fear-relevant stimuli as conditioned stimuli (see Mineka and Öhman, 2002) and in the use of a baseline phase prior to conditioning as a more neutral comparison state (Harrison et al., 2017).

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