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Response from McNish, Gewirtz and Davis

In our recent article examining the role of the hippocampus in contextual fear conditioning, we developed a paradigm which produced contextual freezing and fear-potentiated startle that was specific to a context previously paired with shock[1]. Lesions of the central nucleus of the amygdala blocked both freezing and fear-potentiated startle, consistent with the notion that this structure is critically involved in mediating conditioned fear responses. In contrast, lesions of the dorsal hippocampus disrupted contextual freezing, but had no effect on fear-potentiated startle. Based on these results, we concluded that despite a disruption of freezing, fear to the context was preserved in animals with hippocampal lesions.

Our interpretation of the effects of hippocampal lesions on contextual freezing challenges the notion that context conditioning, like spatial learning, is a hippocampal-dependent task. This notion was encouraged by demonstrations that lesions of the hippocampus disrupted freezing to contextual cues, but had no effect on freezing to explicit cues[2,3]. One interpretation of these findings is that the hippocampus is critically involved in forming complex, polymodal associations, as would be required in forming a representation of context but not in unimodal or 'elemental' associations[4]. An alternative interpretation is that hippocampal lesions enhance motor activity, which preferentially disrupts weak conditioned freezing responses[5]. Given that contextual fear is likely to be less strong than fear to explicit cues[6], one might expect the lesions to have a greater impact on freezing to contextual cues. The commentary by Maren *et al.* attempted to rule out the response competition hypothesis. Furthermore, they propose a model that appears to simulate our data while preserving the central role of the hippocampus in contextual fear conditioning. Below, we will outline why response competition, coupled with a strength of conditioning argument, is a reasonable alternative explanation for the effects of hippocampal lesions on freezing. We will also highlight several problems inherent in the model proposed by Maren *et al*.

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Response competition

Hippocampal lesions increase motor activity

It has frequently been reported that hippocampal lesions increase motor activity. Recently, Maren and Fanselow[7] have reported that across-groups increases in motor activity produced by lesions of the dorsal hippocampus, entorhinal cortex and fimbria-fornix were highly correlated with the disruption of freezing. They have argued that these effects are not causal but reflect a common underlying syndrome, because within a given group the correlations between activity and freezing deficits are poor. However, the lack of significant within-group correlations does not discount a causal relationship. Because the lesions significantly enhanced motor activity, there is a narrower distribution of activity levels within a group than across groups, decreasing the likelihood of finding a significant correlation within a group. The important point is that because their experimental manipulation was at the group level, it is the significant between-groups correlation that is relevant, not the non-significant within-group correlations.

Interestingly, it has recently been reported that excitotoxic dorsal hippocampal lesions produced increases in activity, deficits in freezing and impairments in spatial learning[5]. In contrast, entorhinal cortex lesions also disrupted spatial learning, but had no effect on either activity or freezing. This suggests that there is a closer relationship between motor activity and freezing than between freezing and spatial learning. If the freezing deficits truly reflected a disruption of contextual fear conditioning, one would have expected them to go hand-in-hand with deficits in spatial learning.

In an attempt to rule out a response competition account, Maren *et al*. cite a study showing that local infusion of the *N*-methyl-D-aspartate (NMDA) antagonist DL-2-amino-5-phosphonovalerate (APV) into the dorsal hippocampus during contextual fear conditioning disrupted freezing measured the next day[8]. However, the dose of APV infused into the hippocampus (10 μg) was twice the maximal dose given intraventricularly (5 μg) to block contextual fear conditioning[9]. Because lower, rather than higher, doses of APV given locally would be expected to block conditioning, these data do not rule out the possibility of spread to extra-hippocampal structures or the ventricles. Hence, further studies are required to demonstrate the importance of NMDA receptors in the hippocampus in contextual fear conditioning.

Hippocampal lesions disrupt freezing to explicit cues

An important foundation of Maren *et al.*'s thesis is that: 'dorsal hippocampal lesions attenuate freezing to contextual conditioned stimuli (CSs) but do not alter freezing behavior to discrete CSs'. However, they have recently reported that chemical lesions of the dorsal hippocampus disrupted freezing

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to a contextual CS and to an explicit CS (Ref. 10). While this finding is inconsistent with the original theory, they have argued that the disruption of freezing to the explicit cue reflects a configural component of the explicit cue. Thus, the current theory maintains that any disruption of freezing, whether to an explicit or contextual cue, produced by lesions of the hippocampus reflects a disruption of configural components, whereas any sparing of freezing reflects elemental components of that cue. This logic is circular. Because there seems to be no *a priori* way to predict how much freezing to a given cue is controlled by the elemental or configural components of that cue, the theory seems untestable.

There are also examples where hippocampal lesions have disrupted freezing in situations in which freezing was presumably not under the control of contextual cues. Hippocampal lesions disrupted freezing in the presence of a predator[11,12], freezing to a shock probe and freezing to prevent falling from a narrow ledge[13]. Blanchard *et al.* concluded that hippocampal lesions resulted in a subtle deficit in immobility.

Freezing versus fear

Deficits in freezing do not always reflect deficits in fear conditioning. A light CS elicited less freezing than a tone CS when rats were similarly trained[14], even though several other measures indicated equivalent levels of conditioned fear to the two cues[15]. In addition, a rat's tendency is to escape, rather than freeze, if an escape route is available or if a threat is perceived as imminent[16]. Hence, freezing is a reliable positive indicator of fear; however, the absence of freezing could potentially lead to false negatives.

The model's assumptions

The model proposed by Maren *et al*. makes three assumptions in order to simulate our results. The first assumption is that hippocampal lesions selectively eliminate the use of configural cues. However, there is evidence of preserved configural learning[17,18], contextual control over conditioned responding[19] and context-specific extinction[20] in animals with hippocampal lesions. We agree with the second assumption that freezing has a lower response threshold than fear-potentiated startle. However, by imposing the same ceiling on the two response measures, Maren *et al.* also make the implicit assumption that fear-potentiated startle has a narrower dynamic range (threshold of 25, maximum of 100) than freezing (minimum of 10, maximum of 100). In fact, the opposite is likely to be true. The magnitude of fear-potentiated startle is highly graded[21], and reaches asymptote at relatively high levels of conditioned fear, whereas freezing reaches an asymptote at relatively low levels of conditioned fear. Hence, fear-potentiated startle is likely to have a broader rather than a narrower dynamic range than freezing. Although the third assumption, that fear-potentiated startle is more sensitive to explicit than configural cues is possible, we are not aware of any evidence that some conditioned responses are differentially sensitive to configural versus explicit CSs. Furthermore, based on this assumption, one would still expect some decrease in fear-potentiated startle after hippocampal lesions. In our experiment, we observed absolutely no decrease in fear-potentiated startle to the context in hippocampal-lesioned animals. Such a result would require that fear-potentiated startle is not simply more sensitive to explicit cues, as Maren *et al.* suggest, but is exclusively controlled by explicit cues. There is no evidence to support this stronger version of the assumption. Nonetheless, it appears that this is the actual assumption Maren *et al.* incorporated into their model in order to simulate our data.

Our data demonstrate that fear-potentiated startle is more, not less, sensitive to contextual shifts than freezing. It is more likely that there are common elements versus common configurations between chambers. Fear-potentiated startle was completely eliminated by shifts in context, whereas there was some sparing of freezing. This is inconsistent with the notion that fear-potentiated startle is insensitive to configural cues.

Conclusion

Have we taken the hippocampus out of contextual fear conditioning? We do not believe so. It seems likely that the hippocampus is involved in context conditioning given its role in spatial navigation. However, our data, considered within the broader context of the hippocampal literature, suggest that the hippocampus may not be critical for contextual fear conditioning. At the very least, alternative explanations exist for the deficits in freezing produced by hippocampal lesions. Given the importance of hippocampal function to the study of learning and memory, we believe that these alternative hypotheses warrant further investigation.

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