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The Hippocampus May Support Context Retrieval in One-Shot Learning about Pain

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Review of Wimmer and Büchel

The ability to recall something we encounter only once and unexpectedly—for example, that a food type is poisonous—is crucial for survival. Yet, neuroscientific research in recent decades has been dominated by incremental learning paradigms, relatively neglecting how the brain can learn incidentally from a single experience. In particular, it is striking that the neural basis of one-shot learning about pain has never been investigated, given the value of this ability in our evolutionary repertoire. The hippocampus has been posited as a substrate of single-trial learning (Lee et al., 2015), but evidence suggests that it is not necessary for all forms of such learning (Wimmer and Büchel, 2016; Squire et al., 2021). For example, although the hippocampus was found to mediate explicit choice on the basis of once-encountered associations (Lee et al., 2015), hippocampal lesions did not disrupt the improvement of visual identification performance after a single exposure to a stimulus (Squire et al., 2021). It has therefore been proposed that the hippocampus is necessary only for learning that supports subsequent conscious recollection of the previous experience (known as "declarative" memory), rather than nondeclarative learning, which supports abilities including perceptual skills and habits (Squire et al., 2021). However, an alternative possibility is that the hippocampus contributes, at encoding and retrieval, to any process that associates elements with a context: a feature more common to declarative than nondeclarative memories. Because the role of the hippocampus in one-shot learning may depend on memory content or type, it has been unclear whether the hippocampus is recruited in one-shot learning about pain, and if so, what mechanistic role it plays in this process.

In a recent article published in *The Journal of Neuroscience*, Wimmer and Büchel (2021) investigated one-shot learning about pain in a behavioral and fMRI study. Both experiments had an initial "incidental learning" phase, in which a previously unseen image of a neutral object (e.g., camera, hair brush) was presented on each trial. During the image display, a painful thermal stimulus with either lower heat (lower pain) or higher heat (higher pain) was delivered, after which participants rated pain intensity on a visual analog scale (VAS; scale, 1–8). Participants then took part in a surprise "test" phase that assessed their memory of associations between images and aversive stimuli. In the behavioral study, participants indicated which of two displayed objects was associated with lower heat. In the fMRI study, a neutral object was presented and participants indicated on a similar VAS whether it had been paired with high or low pain, and then whether they recognized the image from the learning phase. Participants performed above chance on all three memory tests.

The authors' primary research question concerned whether pain-related patterns of neural activity from incidental encoding were reactivated at the test phase, and whether this reactivation supported memory retrieval. They performed multivariate analysis to determine whether classifiers trained to discriminate high and low pain in the hippocampus, pain-processing regions, and amygdala in the encoding phase were able to discriminate objects associated with high and low pain when tested on fMRI data from the memory test phase. The hippocampus and pain-processing regions were selected as regions of interest for one-shot learning and pain encoding, respectively; and the amygdala was a control. Notably, classifiers trained on neural data recorded in the learning phase identified significant test phase reactivation of pain-related patterns only in the hippocampus. The authors also performed a control univariate analysis to establish whether the reactivation of patterns across voxels (multivariate activation) was primarily driven by overall activation differences when averaging across voxels in each region (univariate activation). There were no significant overall activation differences between neural responses to objects

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previously associated with high and low pain levels in any of the regions.

Importantly, the extent of reactivation was related to memory retrieval behavior, suggesting that hippocampal reactivation plays a causal rather than epiphenomenal role in memory retrieval (de-Wit et al., 2016). Reactivation in the left anterior hippocampus was correlated with test-pain rating performance across participants, but, surprisingly, hippocampal reactivation was not related to image recognition. This challenges views that the hippocampus primarily supports declarative memory (Tulving, 2002; Squire et al., 2021), but leaves open the possibility that its contribution involves cue–context associations. Thus, this study demonstrates a role for the hippocampus in one-shot learning of pain–visual associations, dissociating between two forms of fMRI data analysis (multivariate reactivation of pain-related patterns, but not univariate amplitude difference, dissociated high and low pain associations in the test phase) and two types of behavioral memory (hippocampal reactivation was related to recapitulation of pain rating but not recognition memory).

To understand the role of the hippocampus in one-shot learning, we must consider its functional specialization in other processes. The hippocampus has been particularly implicated in the association of elements with a context (Nadel, 2008). For example, in contextual fear conditioning, hippocampal lesions do not disrupt learning of freezing responses to an auditory tone that predicts a painful shock (which can be interpreted as a cue–cue association). However, they do disrupt the acquisition of responses to background features of the cage in which the tone–shock associations were observed, which can be understood as a context–cue association (Phillips and LeDoux, 1992). Therefore, a key possibility is that the anterior hippocampal reactivation reflects reactivation of the neural representation of the context of encoding. Area CA1 of the anterior hippocampus contains place cells: neurons whose firing rates are modulated by the position of an animal in space (O'Keefe and Nadel, 1978) and may underpin a cognitive map of the context of an animal (Sanders et al., 2020). Here, "context" may not be environmental: it extends to aspects such as motivational state (Kennedy and Shapiro, 2009), leading to a working definition of context as a situation with a coherent set of expectations and appropriate behaviors (Smith and Bulkin, 2014).

Place cells in the anterior hippocampus have larger place fields than those in the posterior hippocampus, but with similar spatial acuity (Keinath et al., 2014). This equips the anterior hippocampus to perform "pattern completion": the retrieval of holistic experiences given a single cue (Poppenk et al., 2013). Moreover, the reactivation of an ensemble of distributed place cells within the hippocampus can occur spontaneously when re-entering a previously visited context (Guzowski et al., 1999). The distributed reactivation Wimmer and Büchel (2021) identified in the anterior hippocampus may represent a similar reconfiguration of place cell activity, subserving pattern completion in response to a contextual cue. It has previously been shown that the activation of a place cell code can be detected with multivariate but not univariate fMRI analysis (Hassabis et al., 2009), consistent with Wimmer and Büchel's (2021) findings.

Previously, Wimmer and Büchel (2016) found no evidence for hippocampal reactivation in a one-shot learning study using rewarding stimuli. There are two potential reasons why only the pain study (Wimmer and Büchel, 2021) detected reactivation suggestive of pattern completion. First, the test of "value memory" in the pain study used a VAS similar to that used during incidental learning, whereas the reward study tested value memory using a different behavioral procedure from the learning phase. Therefore, the VAS in the pain study may have served as a contextual cue to elicit hippocampal reactivation or the act of rating on a similar VAS may have seemed more akin to re-enacting a previous experience, provoking memory of contextual features of this experience (Lengyel and Dayan, 2008). In either of these cases, although the identified reactivation was not simultaneous with VAS presentation, the intermittent presence of the VAS in the block may have been determinative. A second possible explanation for reactivation solely in the pain study is that the stronger emotional and physical experience associated with pain may have caused participants to perceive it more as a context, whereas small monetary rewards act as cues. Indeed, if what counts as a context is determined by participants' subjective beliefs (Sanders et al., 2020), it may be difficult to pinpoint exactly what caused one case of memory to be contextual and the other not.

An intriguing implication of this context account of the observed hippocampal reactivation would be that pain can act as a form of context during learning. This could point to a new explanation for why, in a previous study, painful stimulation during the encoding of visual information was associated with reduced memory performance for the visual object and reduced hippocampal activation (Forkmann et al., 2013), and, more generally, how learning can be affected in the context of persistent pain (Mansour et al., 2014). Rather than inhibiting learning in general, concurrent pain may have facilitated inference of a different context (Gershman, 2017; Heald et al., 2021), which inhibited memory of the visual stimulus when in a new context. Although Forkmann et al. (2013) interpreted reduced hippocampal univariate activation as evidence for less hippocampal involvement, it should be noted that lower univariate activity can contain increased information content (Kok et al., 2012), including in the hippocampus, where information may be represented in a sparse code with a low mean regional activation (Wixted et al., 2014). Indeed, Wimmer and Büchel (2021) found multivariate but not univariate evidence for hippocampal reactivation.

An outstanding question is the extent to which the hippocampus is involved in longer-term memory representations after one-shot learning. Wimmer and Büchel (2021) tested memory on the same day, but longitudinal research is needed to investigate hippocampal involvement over longer timescales. Tayler et al. (2013) found CA1 place cell contextual reactivation in mice 2 weeks after initial exposure, raising the possibility that hippocampal memory traces last in the longer term. However, it is likely that, ultimately, memory consolidation involves a shift from hippocampal to neocortical substrates (Takashima et al., 2009).

Wimmer and Büchel (2021) make an important contribution to our understanding of the mechanistic role of the hippocampus in incidental one-shot learning; about pain in particular. It is likely that the hippocampal contribution to one-shot learning (in this task) is to facilitate context retrieval, or pattern completion, when receiving information about a cue that was encountered once before. This account may explain why the hippocampus was not related to declarative recognition memory in this task, but is canonically associated more with declarative than nondeclarative memory. Future work should explicitly compare the hippocampal roles in cue and context retrieval after single-trial learning to test the hypothesis

that hippocampal reactivation supports context but not cue retrieval. Experiments should also assess whether hippocampal reactivation underpins memory retrieval with longer intervals between encoding and test phases. Finally, the roles of extra-hippocampal regions in one-shot learning remain vastly underinvestigated and are a promising avenue for future research.

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