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Review article

Heterogeneous representations in the hippocampus☆

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ABSTRACT

The hippocampus is essential for some types of memory, but its specific role remains conjectural. While studies on place cells have supported the hypothesis that the hippocampus provides a spatial substrate for episodic memory, recent engram studies have shown that optogenetic activation of a subset of hippocampal neurons that lack a temporal structure of the spike sequences can also induce memory-associated behavior. In this short review, I discuss the various lines of research that have led to different views of the role of the hippocampus in memory and propose a plausible interpretation of the findings that incorporates two influential theories.

The specific role of the hippocampus in memory is currently unclear. In the human, damage to the medial temporal lobe (MTL) causes a deficit in episodic memory (Scoville and Milner, 1957; Squire, 1992), and activity in the MTL is associated with some components of this type of memory (e.g., Yonelinas et al., 2001). However, past attempts to identify single shared feature of the tasks have failed, making it difficult to infer the specific contribution of the hippocampus to memory (Squire et al., 2004). Recent advances in physiological recordings, imaging, and genetic interventions, including optogenetics and chemogenetics, have significantly progressed our understanding of the hippocampal function through studies on rodents (e.g., Buzsáki, 2015; Colgin, 2016; Josselyn and Tonegawa, 2020; Moser et al., 2015). For example, unit recording has revealed that the activity of the hippocampal pyramidal neurons is strongly modulated by spatial information (O'Keefe, 1976). Some hippocampal neurons known as place cells increase their firing rates when an animal occupies a specific part of the physical environment, and orthogonal sets of place cells participate in this location-specific firing in different environments so that they collectively represent spaces (Fig. 1). Subsequent studies using electrical, pharmacological, or genetic intervention have confirmed the contribution of place cells to spatial memory (e.g., Jadhav et al., 2012; Kentros et al., 1998; McHugh et al., 1996), and O'Keefe and Nadel expanded on this by proposing that the hippocampus provides an allocentric framework for experience that serves as a substrate for episodic memory (the Cognitive Map Theory) (O'Keefe and Nadel, 1978). However, while many studies have supported this idea, it is not mutually exclusive or contradictory to other theories.

Given its necessity for specific types of memory, anatomical structure, and high degree of plasticity within the circuits, the hippocampus has long been assumed to contain physical traces of episodic memory (Neves et al., 2008). Recent engram studies have provided direct tests of this assumption (Tonegawa et al., 2015) by labeling the hippocampal neurons that undergo a form of plastic changes with a probe for optogenetic manipulation and then measuring whether activation or inactivation of the labeled neurons results in the induction or suppression of memory-associated behavior (e.g., Liu et al., 2012; Tanaka et al., 2014). In these studies, immediate early genes (IEGs), such as c-Fos, are used as markers for plastic changes during memory encoding because their activation is triggered by increased (and patterned) neuronal activity and their products play essential roles in plasticity (Okuno, 2011). Therefore, IEG activation would help to determine the type of information that is encoded within the hippocampal neurons. Past studies have revealed patterns of IEG activation in the hippocampus after a memory task and used this to infer the information that is encoded. For example, it is well known that exposure to a novel environment or learning a new spatial task induces greater IEG activation in the hippocampus than exploration in a habituated environment or performing a well-learned spatial task (Hess et al., 1995; Milanovic

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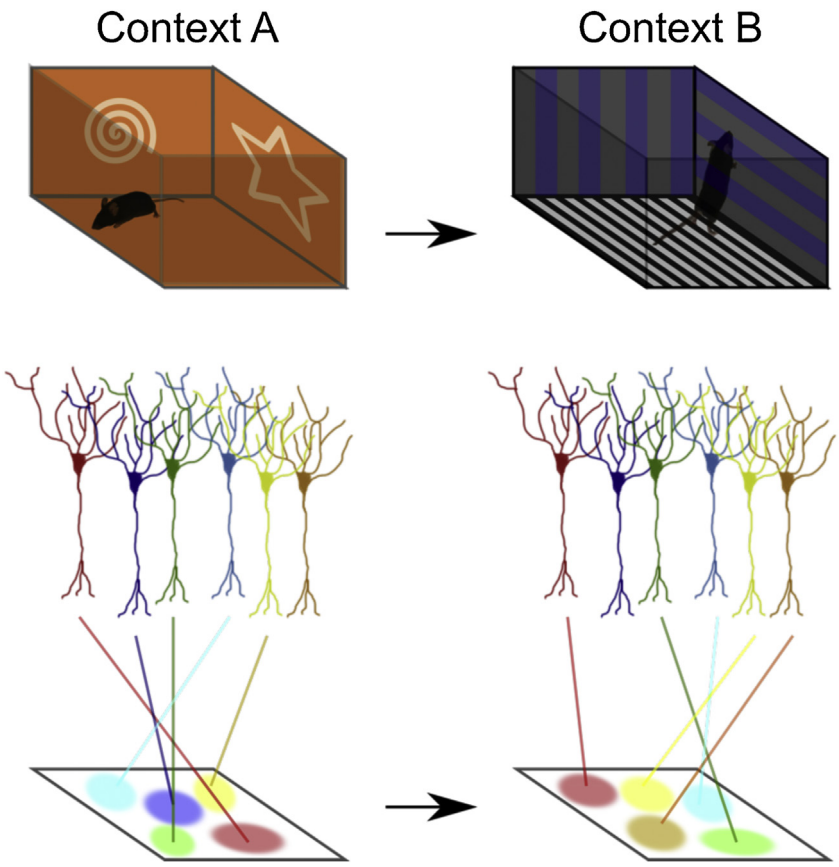

Fig. 1. Distinct subsets of place cells represent different contexts. Some neurons have different firing locations in different contexts, while others show location-specific firing in only one of the environments. In the diagram, pyramidal neurons place cells (middle) are color-coded for their firing locations in the environment (bottom).

et al., 1998). It has also been shown that hippocampal IEGs do not respond to unimodal sensory stimuli presented in a familiar environment (Zhu et al., 1995), supporting the view that the hippocampus encodes contextual and spatial information. Behavioral studies have also shown that the hippocampus contains a conjunctive representation of multimodal information (Rudy and O'Reilly, 2001). For example, in one study, the fear response after an immediate shock in rats increased when the rats were pre-exposed to the context but not when they were pre-exposed to the individual features that made up that context (Fanselow, 1986), and this so-called context pre-exposure facilitation effect (CPFE) is mediated by the hippocampus (Matus-Amat et al., 2004, 2007). These lines of study suggest that the primary role of the hippocampus is to encode multimodal information presented simultaneously, which provides a substrate for the episodic experience. Importantly, this hippocampal representation is not necessarily spatial but rather a contextual representation in a broader sense and cannot be fully explained by the Cognitive Map Theory (discussed below).

The Memory Index Theory explains the hippocampal contribution to memory from a different perspective. It posits that the hippocampal neurons have a unique and continuous interaction with other areas in the brain (Teyler and DiScenna, 1986; Teyler and Rudy, 2007), and that the primary role of the hippocampal memory trace is to index a neocortical representation of the episodic experience so that the trace can (even from a partial input) reactivate the neocortical neurons during memory recall at a later date. A recent experiment suggested that the context representation (or memory engram) in the hippocampus serves as this index. Using c-Fos-tTA mice and optogenetics, Tanaka and colleagues showed that a subset of CA1 neurons that are c-Fos-tagged during contextual fear conditioning are indispensable for later memory recall and, importantly, that the inactivation of these labeled cells also compromises neuronal reactivation in the downstream neocortical areas, suggesting that their activity during recall reinstates the pattern of activity that was present during the original experience (Tanaka et al., 2014). A critical distinction between this theory and the Cognitive Map Theory is that the Memory Index Theory is agnostic to the content of memory encoded in the hippocampal neurons (Teyler and Rudy, 2007). The hippocampal neurons encode a map for the internal representation of experience but not for the external world. Therefore, the Memory Index Theory provides a more convincing explanation of the findings of the CPFE experiment described above because the animal rapidly recalls contextual memory within a short time period without any physical exploration. However, this theory does not provide any explanation on how place cells function as the memory index in the hippocampus.

To reconcile these two theories, Tanaka and colleagues examined the activity of c-Fos-labeled neurons in the CA1 region of the dorsal hippocampus of mice during encoding and recall (Tanaka et al., 2018). In their study, the mice were first allowed to explore a novel context and the activity of the CA1 pyramidal neurons was recorded. A subset of the neurons that expressed c-Fos during this novel experience were then labeled with channelrhodopsin (ChR2) for later optogenetic identification (Cardin et al., 2010). During this contextual encoding, it was found that only a fraction of the place cells were labeled, with more than half of the place cells in the environment failing to express c-Fos. The c-Fos-positive place cells were found to be physiologically distinct from these c-Fos-negative place

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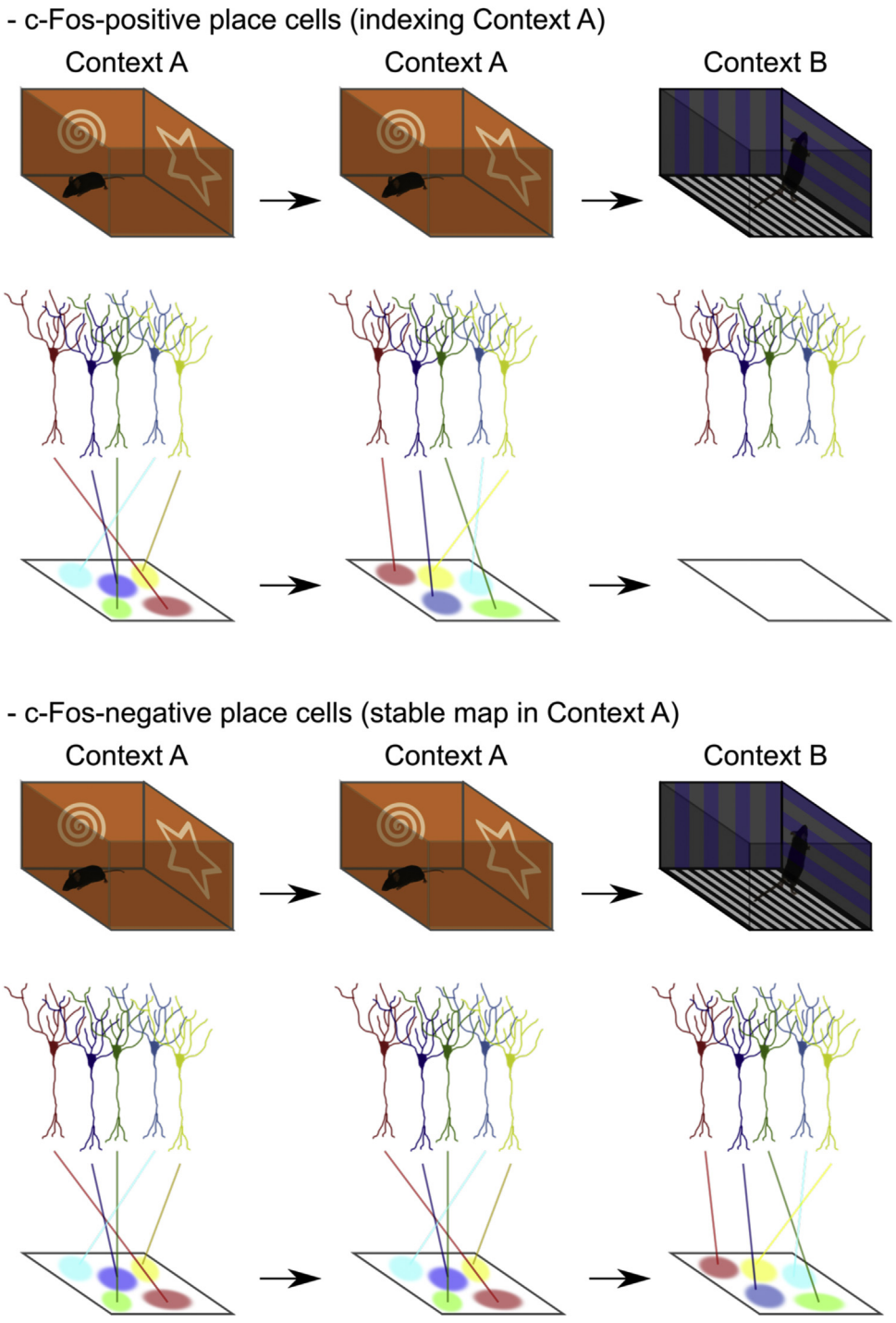

Fig. 2. Different responses of c-Fos-positive and -negative place cells to the encoding context (A) and a new context (B). (Top) c-Fos-positive place cells fire at different locations even when the animal returns to Context A but mostly become silent when the animal explores Context B. (Bottom) c-Fos-negative place cells show a stable spatial map in Context A and remap in Context B, where they remain active.

cells, on average having higher firing rates and smaller amounts of spatial information, burst spikes paced at a theta frequency; theta bursts that are entrained by a different phase of theta oscillation and more likely to occur during fast gamma events. The entrainment to the fast gamma may reflect the involvement of entorhinal inputs and a specific type of synaptic plasticity for the engram formation (Colgin, 2015). Contrary to the expectation that the hippocampal engram stores spatial memory, the spatial map represented by the c-Fos-positive place cells was unstable (Fig. 2). Thus, when mice were returned to the encoding context, the c-Fos-positive place cells changed their firing locations while the c-Fos-negative place cells maintained their original locations. Importantly, these two types of place cells also showed different responses when the mice were placed in a context that differed from the encoding context – while the c-Fos-negative place cells changed their firing locations in this new environment and stayed active, the c-Fos-positive place cells changed their firing rates and in many cases became silent. Finally, context-specific activity occurred in the c-Fos-positive place cells immediately after the animal was placed back in the encoding context, providing a possible substrate for

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the rapid recall of contextual memory. These observations indicate that the hippocampal CA1 region forms two distinct representations during contextual encoding: c-Fos-positive cells that index the contextual identity through their activity and c-Fos-negative cells that stably represent the allocentric frame in the environment. Given these physiological properties, it is plausible to interpret the c-Fos positive and negative representations serve as neuronal substrates for the Memory Index and Cognitive Map, respectively. The c-Fos positive neurons would be able to efficiently select the downstream neurons to be reactivated through its ON/OFF-like activity, and the c-Fos negative place cells would define the relational structure of receptive fields within the cognitive space, which can be reliably retrieved later. Regarding the relation to the downstream neocortical areas, inactivation of c-Fos positive CA1 neurons disrupts neuronal reactivation in the retrosplenial cortex, where is reciprocally connected to numerous neocortical areas (Tanaka et al., 2014; Cowansage et al., 2014). During memory retrieval, c-Fos positive CA1 neurons might reinstate neocortical activities through this hub-like area. Importantly, previous studies have shown that N-methyl-D-aspartate receptor activation during encoding is required to obtain a stable spatial representation (Kentros et al., 1998; McHugh et al., 1996), suggesting that c-Fos-negative place cells are also memory engrams.

Together, these findings suggest that memory trace in the hippocampus, and hence the hippocampal role in memory, is not unitary but rather heterogeneous. Indeed, anatomical, physiological and functional heterogeneities have been reported across the proximal-distal, dorsal-ventral, and anterior-posterior axes of the hippocampal CA1 (i.e., Nakazawa et al., 2016; Fanselow and Dong, 2010; Mizuseki et al., 2011). Soltesz and Losonczy explain the computational advantage of this heterogeneity by their parallel information processing model (Soltesz and Losonczy, 2018). In this model, parallel heterogeneous circuits enable different forms of hippocampal learning, such as goal-directed, trace fear, or contextual fear learning, depending on the task condition. However, a recent study provides an opposite view of these two memory traces (Trouche et al., 2016). It suggests that a stable spatial map represented by c-Fos negatives are tightly linked to a corresponding c-Fos positive index, rather than one of the two being more engaged than the other depending on the cognitive demand during learning. This concomitant nature of the hippocampal memory traces sacrifices its flexibility of information processing. For a more in-depth understanding of this problem, further studies are needed to reveal the functional advantages of having two types of memory traces allocated to discrete groups of CA1 neurons, and their functional interactions between the two and also with other areas in the brain.

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References

Buzsáki, G., 2015. Hippocampal sharp wave-ripple: a cognitive biomarker for episodic memory and planning. Hippocampus 25 (10), 1073–1188, http://dx.doi.org/10.1002/hipo.22488.

Cardin, J.A., Carlén, M., Meletis, K., Knoblich, U., Zhang, F., Deisseroth, K., et al., 2010. Targeted optogenetic stimulation and recording of neurons in vivo using cell-type-specific expression of Channelrhodopsin-2. Nat. Protoc. 5 (2), 247–254, http://dx.doi.org/10.1038/nprot.2009.228.

Colgin, L.L., 2015. Do slow and fast gamma rhythms correspond to distinct functional states in the hippocampal network? Brain Res. 1621 (September 24), 309–315, http://dx.doi.org/10.1016/j.brainres.2015.01.005.

Colgin, L.L., 2016. Rhythms of the hippocampal network. Nat. Rev. Neurosci. 17 (4), 239–249, http://dx.doi.org/10.1038/nrn.2016.21.

Cowansage, K.K., Shuman, T., Dillingham, B.C., Chang, A., Golshani, P., Mayford, M., 2014. Direct reactivation of a coherent neocortical memory of context. Neuron 84 (2), 432–441, http://dx.doi.org/10.1016/j.neuron.2014.09.022.

Fanselow, M.S., 1986. Associative vs topographical accounts of the immediate shock freezing deficit in rats - implications for the response selection-rules governing species-specific defensive reactions. Learn. Motiv. 17 (1), 16–39.

Fanselow, M.S., Dong, H.-W., 2010. Are The Dorsal and Ventral Hippocampus functionally distinct structures? Neuron 14 (1), 7, http://dx.doi.org/10.1016/j.neuron.2009.11.031, 65.

Hess, U.S., Lynch, G., Gall, C.M., 1995. Regional patterns of c-fos mRNA expression in rat hippocampus following exploration of a novel environment versus performance of a well-learned discrimination. J. Neurosci. 15 (12), 7796–7809.

Jadhav, S.P., Kemere, C., German, P.W., Frank, L.M., 2012. Awake hippocampal sharp-wave ripples support spatial memory. Science (New York, NY) 336 (6087), 1454–1458, http://dx.doi.org/10.1126/science.1217230.

Josselyn, S.A., Tonegawa, S., 2020. Memory engrams: recalling the past and imagining the future. Science (New York, NY) 367 (6473), eaaw4325, http://dx.doi.org/10.1126/science.aaw4325.

Kentros, C., Hargreaves, E., Hawkins, R.D., Kandel, E.R., Shapiro, M., Muller, R.V., 1998. Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. Science (New York, NY) 280 (5372), 2121–2126.

Liu, X., Ramirez, S., Pang, P.T., Puryear, C.B., Govindarajan, A., Deisseroth, K., Tonegawa, S., 2012. Optogenetic stimulation of a hippocampal engram activates fear memory recall. Nature 484 (7394), 381–385, http://dx.doi.org/10.1038/nature11028.

Matus-Amat, P., Higgins, E.A., Barrientos, R.M., Rudy, J.W., 2004. The role of the dorsal hippocampus in the acquisition and retrieval of context memory representations. J. Neurosci. 24 (10), 2431–2439, http://dx.doi.org/10.1523/JNEUROSCI.1598-03.2004.

Matus-Amat, P., Higgins, E.A., Sprunger, D., Wright-Hardesty, K., Rudy, J.W., 2007. The role of dorsal hippocampus and basolateral amygdala NMDA receptors in the acquisition and retrieval of context and contextual fear memories. Behav. Neurosci. 121 (4), 721–731, http://dx.doi.org/10.1037/0735-7044.121.4.721.

McHugh, T.J., Blum, K.I., Tsien, J.Z., Tonegawa, S., Wilson, M.A., 1996. Impaired hippocampal representation of space in CA1-specific NMDAR1 knockout mice. Cell 87 (7), 1339–1349.

Milanovic, S., Radulovic, J., Laban, O., Stiedl, O., Henn, F., Spiess, J., 1998. Production of the Fos proteinafter contextual fear conditioning of C57BL/6N mice. Brain Res. 784 (1–2), 37–47.

Mizuseki, K., Diba, K., Pastalkova, E., Buzsáki, G., 2011. Hippocampal CA1 pyramidal cells form functionally distinct sublayers. Nat. Neurosci. 14 (9), 1174–1181.

Moser, M.-B., Rowland, D.C., Moser, E.I., 2015. Place cells, grid cells, and memory. Cold Spring Harb. Perspect. Biol. 7 (2), a021808, http://dx.doi.org/10.1101/cshperspect.a021808.

Nakazawa, Y., Pevzner, A., Tanaka, K.Z., Wiltgen, B.J., 2016. Memory retrieval along the proximodistal axis of CA1. Hippocampus 26 (9), 1140–1148.

Neves, G., Cooke, S.F., Bliss, T.V.P., 2008. Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. Nat. Rev. Neurosci. 9 (1), 65–75, http://dx.doi.org/10.1038/nrn2303.

O'Keefe, J., 1976. Place units in the hippocampus of the freely moving rat. Exp. Neurol. 51 (1), 78–109.

O'Keefe, J., Nadel, L., 1978. The Hippocampus As a Cognitive Map. Oxford University Press, USA.

Okuno, H., 2011. Regulation and function of immediate-early genes in the brain: beyond neuronal activity markers. Neurosci. Res. 69 (3), 175–186, http://dx.doi.org/10.1016/j.neures.2010.12.007.

Rudy, J.W., O'Reilly, R.C., 2001. Conjunctive representations, the hippocampus, and contextual fear conditioning. Cogn. Affect. Behav. Neurosci. 1 (1), 66–82.

Scoville, W.B., Milner, B., 1957. Loss of recent memory after bilateral hippocampal lesions. J. Neurol. Neurosurg. Psychiatr. 20 (1), 11–21.

Soltesz, I., Losonczy, A., 2018. CA1 pyramidal cell diversity enabling parallel information processing in the hippocampus. Nat. Neurosci. 21 (4), 484–493, http://dx.doi.org/10.1038/s41593-018-0118-0.

Squire, L.R., 1992. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol. Rev. 99 (2), 195–231.

Squire, L.R., Stark, C.E.L., Clark, R.E., 2004. The medial temporal lobe. Annu. Rev. Neurosci. 27, 279–306, http://dx.doi.org/10.1146/annurev.neuro.27.070203.144130.

Tanaka, K.Z., Pevzner, A., Hamidi, A.B., Nakazawa, Y., Graham, J., Wiltgen, B.J., 2014. Cortical representations are reinstated by the Hippocampus during memory retrieval. Neuron 84 (2), 347–354, http://dx.doi.org/10.1016/j.neuron.2014.09.037.

Tanaka, K.Z., He, H., Tomar, A., Niisato, K., Huang, A.J.Y., McHugh, T.J., 2018. The hippocampal engram maps experience but not place. Science (New York, NY) 361 (6400), 392–397, http://dx.doi.org/10.1126/science.aat5397.

Teyler, T.J., DiScenna, P., 1986. The hippocampal memory indexing theory. Behav. Neurosci. 100 (2), 147–154.

Teyler, T.J., Rudy, J.W., 2007. The hippocampal indexing theory and episodic memory: updating the index. Hippocampus 17 (12), 1158–1169, http://dx.doi.org/10.1002/hipo.20350.

Tonegawa, S., Liu, X., Ramirez, S., Redondo, R., 2015. Memory engram cells have come of age. Neuron 87 (5), 918–931, http://dx.doi.org/10.1016/j.neuron.2015.08.002.

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Trouche, S., Perestenko, P.V., van de Ven, G.M., Bratley, C.T., McNamara, C.G., Campo-Urriza, N., Lucas Black, S., Reijmers, L.G., Dupret, D., 2016. Recoding a cocaine-place memory engram to a neutral engram in the hippocampus. Nat. Neurosci. 19, 564–567.

Yonelinas, A.P., Hopfinger, J.B., Buonocore, M.H., Kroll, N.E., Baynes, K., 2001. Hippocampal, parahippocampal and occipital-temporal contributions to associative and item recognition memory: an fMRI study. Neuroreport 12 (2), 359–363, http://dx.doi.org/10.1097/00001756-200102120-00035.

Zhu, X.O., Brown, M.W., McCabe, B.J., Aggleton, J.P., 1995. Effects of the novelty or familiarity of visual stimuli on the expression of the immediate early gene c-fos in rat brain. Neuroscience 69 (3), 821–829, http://dx.doi.org/10.1016/0306-4522(95)00320-i.

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