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Pattern and predictability in memory formation: From molecular mechanisms to clinical relevance

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ABSTRACT

Most long-term memories are formed as a consequence of multiple experiences. The temporal spacing of these experiences is of considerable importance: experiences distributed over time (spaced training) are more easily encoded and remembered than either closely spaced experiences, or a single prolonged experience (massed training). In this article, we first review findings from studies in animal model systems that examine the cellular and molecular properties of the neurons and circuits in the brain that underlie training pattern sensitivity during long-term memory (LTM) formation. We next focus on recent findings which have begun to elucidate the mechanisms that support inter-trial interactions during the induction of LTM. Finally, we consider the implications of these findings for developing therapeutic strategies to address questions of direct clinical relevance.

1. Introduction

All animals must use their experience to create a statistical model of their world. This model is driven by both pattern and predictability. The regularity (or pattern) of an experience is predictive of the likelihood of an encounter with the same or related experiences in the future, and therefore facilitates the acquisition and maintenance of adaptive behavior. The maintenance of such a predictive model depends on the formation of long-term memory (LTM). Yet not all repeated experiences are retained in LTM. The timing of experiences is critical. In psychological terms, the benefit to LTM induction of temporally distributed experiences (trials), compared to more closely spaced trials, is often termed *the spacing effect* and can be traced to the earliest formal studies of human learning and memory by Hermann Ebbinghaus (1885/1913). Since these seminal observations more than a century ago, it has become increasingly evident that the spacing effect is a ubiquitous phenomenon that governs LTM formation in a wide range of species and across a wide variety of tasks. Yet even after decades of study, we still understand relatively little about the properties of neural circuits in the brain that determine the benefit of spaced training. In this review we will briefly discuss major findings that elucidate some of the cellular and molecular mechanisms that can, at least in principle, contribute to the spacing effect. We will then focus on recent studies that provide novel and fundamental insights into how effective spacing intervals are determined and may benefit LTM formation. Finally, we conclude with a discussion of the implications of experimental studies for the development of effective learning strategies in humans, as well as the potential for these studies to inform questions of direct clinical relevance.

2. General principles of the spacing effect

The benefit of spaced training to LTM formation is widely observed in both vertebrate and invertebrate model systems, and provides striking parallels to the general principles observed in humans. The spacing effect in LTM is observed across a variety of tasks, including spatial reference memory (Bolding & Rudy, 2006), working memory (Klapdor & Van Der Staay, 1998), appetitive associative conditioning (Colomb, Kaiser, Chabaud, & Preat, 2009), aversive associative conditioning (Amano & Maruyama, 2011; Williams, Frame, & LoLordo, 1991; Yin et al., 1994) and both sensitization and habituation (Carew, Pinsker, & Kandel, 1972; Pinsker, Carew, Hening, & Kandel, 1973; Sutton, Ide, Masters, & Carew, 2002). Effective training intervals appear to be task specific and are controlled by a number of factors, including the retention interval examined (e.g., Beck, Schroeder, & Davis, 2000; Gerber, Wustenberg, Schutz, & Menzel, 1998) and the relationship between trial duration and trial spacing (Gibbon, Baldock, Locurto, Gold, & Terrace, 1977). Finally, although a sufficient spacing of training trials is necessary to benefit LTM induction (with effective training intervals ranging from minutes to days; see Parsons & Davis, 2012), trials can of course also be spaced too far apart to support LTM acquisition (Bolding & Rudy, 2006; Gibbon et al., 1977; Parsons & Davis, 2012; Philips, Tzvetkova, & Carew, 2007). Thus, the benefit of spaced training is non-monotonic, in agreement with

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studies in humans (Cepeda, Pashler, Vul, Wixted, & Rohrer, 2006; Ebbinghaus, 1885/1913).

Interestingly, although there is a general trend in both the human and animal literature describing a benefit from repeated spaced training trials, there is a large body of work studying LTM which forms following a single training session, so-called "flashbulb" memories (Diamond, Campbell, Park, Halonen, & Zoladz, 2007; van Giezen, Arensman, Spinhoven, & Wolters, 2005). Is this learning different from that which develops over repeated experiences? One-trial memories typically develop from emotionally salient events and may indeed rely on mechanisms that are different from those recruited during multi-trial learning (Irvine, von Hertzen, Plattner, & Giese, 2006; Radwanska et al., 2011). However, memory deficits on one-trial cued fear and passive avoidance tasks in mutant mice (that are alphaCAMKII autophosphorylation-deficient) can be rescued by providing additional spaced training trials (Irvine, Vernon, & Giese, 2005). Thus, the possibility exists that even one-trial learning tasks can benefit from mechanisms that subserve LTM formation across spaced training.

3. Cellular and molecular correlates of the spacing effect

Both vertebrates and invertebrates express memory across multiple temporal domains. Each domain has unique cellular and molecular mechanisms that support its induction. Short-term memory (STM) typically develops following a single experience (training trial), lasts on the order of minutes, and relies on the transient modification of pre-existing proteins to establish short-lasting plasticity within underlying neural circuits (Alkon & Naito, 1986; Barondes, 1970; Castellucci, Blumenfeld, Goelet, & Kandel, 1989; Scheibenstock, Krygier, Haque, Syed, & Lukowiak, 2002; Wittstock, Kaatz, & Menzel, 1993; Xia, Feng, & Guo, 1998). Following multiple training trials, both intermediate-term memory (ITM, lasting several hours) and LTM (lasting $\geqslant$24 h) are established. ITM induction requires ongoing protein synthesis, but does not require new gene transcription (Lukowiak, Adatia, Krygier, & Syed, 2000; Lyons, Green, & Eskin, 2008; Sangha, Scheibenstock, McComb, & Lukowiak, 2003; Stough, Shobe, & Carew, 2006; Sutton, Masters, Bagnall, & Carew, 2001). In contrast, LTM requires not only protein synthesis, but also gene expression to stabilize the new growth and enhanced cellular and synaptic plasticity required for LTM expression (Bailey, 1999; Bailey, Bartsch, & Kandel, 1996; Castellucci et al., 1989; Mozzachiodi, Lorenzetti, Baxter, & Byrne, 2008; Sangha et al., 2003; Sutton et al., 2001; Tully, Preat, Boynton, & Del Vecchio, 1994; Wustenberg, Gerber, & Menzel, 1998).

The spacing effect does not appear to regulate the acquisition or development of STM, but strongly regulates the induction of LTM in a variety of learning tasks in a wide range of species, including pigeon (Gibbon et al., 1977), rodent (Bolding & Rudy, 2006; Klapdor & Van Der Staay, 1998; Williams et al., 1991), honeybee (Gerber et al., 1998), *Drosophila* (Tully et al., 1994), *Hermissenda* (Rogers, Talk, & Matzel, 1994), *Lymnaea* (Lukowiak, Cotter, Westly, Ringseis, & Spencer, 1998), and *Aplysia* (Carew et al., 1972). The effect of training pattern on the formation of ITM is less well studied, but has shown to be of benefit in some cases (Sutton et al., 2002). Not surprisingly, spaced training is better than massed training at recruiting the cellular, molecular and structural signatures of LTM (for recent comprehensive reviews see Barco, Bailey, & Kandel, 2006; Lynch, Kramar, Babayan, Rumbaugh, & Gall, 2013; Naqib, Sossin, & Farah, 2012).

3.1. Cellular correlates

In vertebrate studies, the long-term potentiation (LTP) of synaptic signaling is the most often studied cellular correlate of LTM (although there are several instances described in which LTP induction and LTM induction are not correlated: Barnes, 1995; Pineda et al., 2004, and Shors & Matzel, 1997). LTP is observed at synapses in multiple brain regions, but LTP of the CA3 Schaffer collateral synapses onto area CA1 pyramidal neurons in the hippocampus has been most frequently studied (Bliss & Collingridge, 1993; Malenka & Bear, 2004). LTP induction at CA3/CA1 synapses and LTM share many mechanistic similarities, including the ability to be strengthened across spaced training and a sensitivity to the patterning of spaced training trials (Abraham, Logan, Greenwood, & Dragunow, 2002; Huang & Kandel, 1994; Kramar et al., 2012; Malenka, 1994; Winder, Mansuy, Osman, Moallem, & Kandel, 1998). At the molecular level, the requirements for a form of long-lasting LTP (L-LTP) are similar to those for LTM: both require cAMP, cAMP-dependent protein kinase A (PKA), the extracellular signal-regulated protein kinase (ERK) of the mitogen-activated protein kinase superfamily (hereafter referred to as MAPK) and CREB signaling (for review see Barco et al., 2006). Moreover, manipulations that remove inhibitory constraints on PKA, MAPK and CREB activation, support the induction of LTP and LTM with a reduced number of trials (Barad, Bourtchouladze, Winder, Golan, & Kandel, 1998; Genoux et al., 2002; Malleret et al., 2001). In studies in invertebrate model systems, where clear links between behavior and cellular signaling can be established, similar conclusions have been drawn between the training pattern sensitivity for the induction of structural plasticity (Wainwright, Zhang, Byrne, & Cleary, 2002), neuronal excitability (Mozzachiodi et al., 2008; Rogers et al., 1994) and synaptic plasticity (Mauelshagen, Sherff, & Carew, 1998) and LTM. There are several excellent recent reviews in this general area (Barco et al., 2006; Mayford, Siegelbaum, & Kandel, 2012; Mozzachiodi & Byrne, 2010; Naqib et al., 2012).

3.2. CREB

A conserved molecular target of the spacing effect appears to be the differential recruitment of the cAMP response element binding protein (CREB) signaling and CREB-mediated transcription by spaced, but not massed training patterns (reviewed in Naqib et al., 2012; Silva, Kogan, Frankland, & Kida, 1998; Yin & Tully, 1996). CREB-mediated transcription is a critical requirement for the development of long-lasting plasticity and LTM in many systems (Dash, Hochner, & Kandel, 1990; Pittenger et al., 2002; Taubenfeld, Milekic, Monti, & Alberini, 2001) and is upstream of the synthesis of cytoplasmic effectors such as synapsin I (Hart et al., 2011) as well as subsequent nuclear signaling mediated by the recruitment of genes which encode for additional transcription factors important for memory consolidation, including C/EBP (Alberini, Ghirardi, Metz, & Kandel, 1994; Taubenfeld et al., 2001) and CREB itself (Liu, Cleary, & Byrne, 2011). Removing the inhibitory constraints on CREB activation or overexpressing CREB during learning can support the formation of long-lasting forms of synaptic plasticity and LTM with reduced training trials (Bartsch, Casadio, Karl, Serodio, & Kandel, 1998; Bartsch et al., 1995; Genoux et al., 2002; Malleret et al., 2001; Yin, Del Vecchio, Zhou, & Tully, 1995). Thus, CREB recruitment is an important and highly conserved mechanism that contributes to establishing the training pattern requirements for memory formation.

Importantly, CREB phosphorylation on ser133 (Gonzalez & Montminy, 1989) is not always sufficient to induce its transcriptional activity. The recruitment of transcriptional coactivators such as the CREB-binding protein (CBP) and the CREB-regulated transcriptional coactivator 1 (CRTC1) help to regulate CREB-dependent LTP and LTM formation (Ch'ng et al., 2012; Hirano et al., 2013; Kovacs et al., 2007; Wood et al., 2005; Zhou et al., 2006). Evidence from LTP studies in rat has implicated CRTC1 in pattern detection (Zhou et al., 2006). Overexpression of CRCT1 is sufficient to lower the