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Review

In search of a recognition memory engram

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A R T I C L E I N F O

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A large body of data from human and animal studies using psychological, recording, imaging, and lesion techniques indicates that recognition memory involves at least two separable processes: familiarity discrimination and recollection. Familiarity discrimination for individual visual stimuli seems to be effected by a system centred on the perirhinal cortex of the temporal lobe. The fundamental change that encodes prior occurrence within the perirhinal cortex is a reduction in the responses of neurones when a stimulus is repeated. Neuronal network modelling indicates that a system based on such a change in responsiveness is potentially highly efficient in information theoretic terms. A review is given of findings indicating that perirhinal cortex acts as a storage site for recognition memory of objects and that such storage depends upon processes producing synaptic weakening.

Contents

1. Introduction

Gabriel Horn, my long-term mentor, was an inspiration, both personally and through his research, to me and many others. His originality and clarity of thought made possible major, path-finding advances in research into the neural basis of memory. This review will make brief mention of parallels in approach between Gabriel's work in search of the memory engram underlying imprinting in the chick while describing research into the role of perirhinal cortex as a storage site for recognition memory.

A large body of data from human and animal studies using psychological, recording, imaging, and lesion techniques indicates that recognition memory involves at least two separable processes: familiarity discrimination and recollection, and that perirhinal cortex is particularly concerned with familiarity discrimination for individual items, although some disagreement remains (see for reviews and recent work: Brown and Aggleton, 2001; Brown et al., 2010; Clark and Squire, 2010, 2013; Dede et al., 2014; Eichenbaum et al., 2007; Guderian et al., 2011; Kim et al., 2014; Lech and Suchan, 2013; Martin et al., 2013; McNulty et al., 2012; Miyamoto et al., 2014; Ranganath and Ritchey, 2012; Wang et al., 2013; Warburton and Brown, 2010; Watson and Lee, 2013; Westerberg et al., 2013; Winters et al., 2008). There is wide agreement (see above references) that more complex aspects of recognition memory including recollective, contextual, associative and spatial aspects

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of recognition memory rely on the hippocampus. This review will focus on the familiarity discrimination component of recognition memory (has an item been experienced previously or not?) and what is known of neural changes in the perirhinal cortex of the temporal lobe that have been associated with such learning. Analysis of potential neural changes underlying the learning has mainly been carried out in rodents. Fortunately, there is good evidence to indicate that similar brain regions and potentially similar mechanisms are found also in primates (as discussed further below).

Recognition memory requires judgements concerning the physical characteristics of a stimulus (or event) and the prior occurrence of that stimulus (event). Although recognition memory relies on a stimulus being identifiable (at the least that its physical characteristics can be perceived), judgements of prior occurrence themselves do not necessarily involve the new learning of stimulus characteristics. Judgements of prior occurrence can be made for a stimulus whose physical characteristics (identity) have already been learned ('when did you last see your father?'). Similarly, judgements of stimulus identity may be made without requiring consideration of prior occurrence ('which of these two stimuli in front of you is a dog and which a cat?'). Accordingly, judgements of stimulus identity and of prior occurrence are potentially separable processes, although they are strongly interlinked. Manipulating the confusability of stimuli and the length of time between their appearances will alter the difficulty of both identity and recognition memory judgements. Mechanisms underlying judgement of prior occurrence are most readily studied when perceptual discrimination is made easy.

Imprinting relies on a bird recognising a specific stimulus (in nature, the mother hen). However, although the learning necessarily implies a record within the brain of the bird's prior experience of the imprinted stimulus, what is standardly measured in the laboratory is the bird's discrimination of the highly familiar imprinted stimulus from another, less familiar ('novel') stimulus. As the imprinted and alternative stimuli are repeatedly presented, the discrimination between them is likely to rely more on the learned physical characteristics of the imprinted stimulus (i.e. its identity) than its relative familiarity. Correspondingly, the observed brain changes produced by imprinting are likely mainly to concern learning to recognise the physical characteristics of the stimulus (together with its social/emotional import), i.e. the ability to identify the imprinted stimulus, rather than when it was last seen.

The research to be reported involving perirhinal cortex is concerned with the learning underlying judgements of the prior occurrence of a stimulus, chiefly its relative familiarity, rather than learning to identify that stimulus. *Relative* familiarity is a more conservative term than absolute familiarity as any given stimulus typically shares features with other, previously experienced stimuli so that judgements are more probably of relative unfamiliarity rather than absolute novelty. Notably, the memory to be considered is dependent upon single rather than multiple exposure learning. In the case of perirhinal cortex, the potential separation of learning types is an important issue because perirhinal cortex appears to be involved in both types of learning: multi-exposure perceptual and single-exposure prior occurrence (Bartko et al., 2007a,b, 2010; Brown and Aggleton, 2001; Buckley and Gaffan, 1998, 2006; Bussey and Saksida, 2002, 2005; Bussey et al., 2002; Clark and Squire, 2010; Eichenbaum et al., 2007; Guderian et al., 2011; Murray and Bussey, 1999a; Murray et al., 2007; Norman and Eacott, 2004; Warburton and Brown, 2010; Winters et al., 2008). If familiarity judgements are to be studied, it is important that the stimuli to be discriminated are seen infrequently – otherwise the subject is more likely to rely on information concerning recency or context in making decisions. In animal research on familiarity discrimination a 'familiar' stimulus may have been encountered only once previously and a 'novel' stimulus is likely never to have been experienced previously, and certainly not at all recently. It should be noted that this usage differs from much research with human subjects where the items presented (e.g. words or pictures of common objects) are often familiar (although unlikely to have been encountered recently).

2. Localising the engram

Gabriel's early work on imprinting was aimed at finding where in the chick brain learning-related changes occurred. Autoradiography was used to detect biochemical changes indicating brain regions where learning was occurring during imprinting (Bateson et al., 1973; Horn et al., 1971; Rose et al., 1970); this was then followed up with autoradiographic imaging (Horn et al., 1979). In the case of familiarity discrimination, the initial localisation of the critical region was a result rather of serendipity than a systematic approach (Brown et al., 1987). However, subsequent research used immunohistochemical imaging to identify regions showing familiarity-related changes. Such work has recently been reviewed (Aggleton et al., 2012); more recent papers include (Barbosa et al., 2013; Beer et al., 2013).

The central difficulty in localising an engram is that of separating incidental and non-specific changes from those that encode the memory itself. Many changes occur in the brain when something is learned; only a few of these changes are specific to registration of the particular memory itself. For the chick considerable ingenuity was engaged in a series of experiments that isolated changes exclusively related to learning from those arising from sensory stimulation, behavioural (motor) output, motivation, or changes in emotional or endocrinological state, or in alertness and attention (Bateson et al., 1973; Horn, 1985; Horn et al., 1971).

A variety of techniques have been used to provide similar exclusions in the case of recognition memory. One such is the paired viewing procedure (Zhu et al., 1996). A rat is taught that it can receive juice by maintaining its snout in a hole. While in this position the rat is shown successively a series of pairs of objects (early experiments) or pictures on a computer screen (later experiments), with one of each pair being visible only by the left eye, the other only by the right. Juice is delivered just before the pictures disappear. Over several days the rat is acclimatised to the procedure and a particular series of pictures is shown repeatedly with the intention of making them familiar. The rat also sees novel pictures, so that it becomes used to seeing both a novel and familiar picture at the same time. At test on the final day, the familiar set of pictures is displayed to one eye while simultaneously the other eye sees a series of novel pictures. This task has no behavioural contingency beyond the rat maintaining its viewing position; consequently, behaviour is the same for both familiar and simultaneously displayed novel pictures, as is the rat's level of alertness, and its motivational, emotional and endocrinological states. The association of juice delivery with the pictures is important for maintaining the rat's interest in viewing the pictures, though it raises the possibility that the familiar pictures may gain a stronger association with reward than the novel. How the rat's attention might be directed during viewing is unknown. Sensory input is matched as the same number of novel and familiar pictures are seen and, across rats, the sets of novel and familiar pictures are counterbalanced so a novel picture for one rat is familiar for the next, and vice versa. Similarly, across rats the eye viewing the novel pictures is also counterbalanced. Brain activation is then compared between the two hemispheres, the rat becoming its own control. By displaying the pictures in the monocular fields of each eye, information initially passes to the opposite hemisphere, for novel pictures on one side and familiar on the other. Fortuitously, most of the information does not re-cross to the opposite hemisphere, so novel-familiar differences are indeed found without a requirement to sever the corpus callosum.

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