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Neural mechanisms supporting the extraction of general knowledge across episodic memories

Carly C.G. Sweegers [a,b,*], Atsuko Takashima [c,d], Guillén Fernández [c,e], Lucia M. Talamini [a,b]

[a] Department of Psychology, University of Amsterdam, Netherlands
[b] Cognitive Science Center Amsterdam, University of Amsterdam, Netherlands
[c] Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Netherlands
[d] Behavioural Science Institute, Radboud University Nijmegen, Netherlands
[e] Department of Cognitive Neuroscience, Radboud University Medical Centre, Netherlands

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ABSTRACT

General knowledge acquisition entails the extraction of statistical regularities from the environment. At high levels of complexity, this may involve the extraction, and consolidation, of associative regularities across event memories. The underlying neural mechanisms would likely involve a hippocampo-neocortical dialog, as proposed previously for system-level consolidation. To test these hypotheses, we assessed possible differences in consolidation between associative memories containing cross-episodic regularities and unique associative memories. Subjects learned face–location associations, half of which responded to complex regularities regarding the combination of facial features and locations, whereas the other half did not. Importantly, regularities could only be extracted over hippocampus-encoded, associative aspects of the items. Memory was assessed both immediately after encoding and 48 h later, under fMRI acquisition. Our results suggest that processes related to system-level reorganization occur preferentially for regular associations across episodes. Moreover, the build-up of general knowledge regarding regular associations appears to involve the coordinated activity of the hippocampus and mediofrontal regions. The putative cross-talk between these two regions might support a mechanism for regularity extraction. These findings suggest that the consolidation of cross-episodic regularities may be a key mechanism underlying general knowledge acquisition.

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Introduction

The brain stores information about the statistical properties of the environment at all levels of complexity. This entails the extraction of regularities over spatially and temporally discontinuous events to form perceptual categories, sensorimotor routines and more complex forms of concepts and relations. The resulting, highly structured, information system is termed 'semantic memory' (Patterson et al., 2007; Tulving, 1985) and is thought to depend on networks comprising widespread cortical regions (Binder et al., 2009; Martin and Chao, 2001). Various observations suggest that the formation of semantic memories depends in large part on episodic memory (Moscovitch et al., 2005; Rosenbaum et al., 2001; but see Gardiner et al., 2008 for an opposite viewpoint) and an intact hippocampus (Bayley and Squire, 2005; Hayman et al., 1993; Manns et al., 2003). Episodic memory refers to memory for events and situations, organized in an autobiographical stream, and rich in contextual information (Tulving, 1983). This type of memory depends on the hippocampus to quickly encode the spatial and temporal relations between event components represented in

distributed cortical regions (Burgess et al., 2002; Lisman et al., 2005; Meeter et al., 2004; Nadel and Moscovitch, 1997; Squire, 1992). The mechanisms underlying semantic memory formation may therefore involve some form of hippocampo-neocortical dialog, whereby only certain aspects of the original episodes are recoded to hippocampus-independent cortical representations.

Hippocampal–neocortical interactions have previously been shown to underlie system-level consolidation, the process through which hippocampus-dependent memories, over time, acquire a more cortically based, and more stable representation. Here, we propose that one principle governing this process relates to the extraction of regular associations over episodes. Indeed, memory representations reflecting such regularities may be consolidated preferentially at the expense of those reflecting incidental associations. This implies that different components of episodic memories may undergo different consolidation trajectories, depending on the stability of the associations they reflect and, therewith, the relevance of these associations in the long-term. In other words, memory traces may not be consolidated in their original form, but in a reduced state that reflects environmental regularities.

If extraction of regularities over hippocampus-dependent memory traces indeed occurs, it will likely involve the contemporaneous (re)activation of multiple episodic memories and detection of associative

* Corresponding author at: Weesperplein 4, 1018 XA Amsterdam, Netherlands.
  E-mail address: sweegers@gmail.com (C.C.G. Sweegers).

overlap. An area that may play a central role in such processing is the prefrontal cortex (PFC). Its well-known role in memory function relates to the organization of information to be memorized and the use of such organization in retrieval strategies (Blumenfeld and Ranganath, 2007; Otani, 2004). While in most pertaining experiments these functions regarded object categorization, the prefrontal cortex might play a similar role in the organization of episodic memories according to associative similarities. However, in the latter case, the necessary reactivation of stored episodic memory traces would plausibly require interplay of the prefrontal cortex with the hippocampus. The medial prefrontal cortex (mPFC) might be particularly important as lesions to this area impair category formation (Drewe, 1974) and shifting between response rules (Birrell and Brown, 2000). Moreover, since the mPFC receives monosynaptic input from the hippocampus, a direct portal for hippocampo-prefrontal communication is available (Swanson, 1981; Thierry et al., 2000). In line with this notion, several studies implicate hippocampo-mPFC communication in rule and schema learning (Benchenane et al., 2010; Kumaran et al., 2009; van Kesteren et al., 2010), which also involve interactions of new associative input with already stored information.

In view of the above, we expect that hippocampus–mPFC interactions might play a major role in the extraction of regularities over episodes. We, furthermore, hypothesize that system-level consolidation will be particularly evident for associations containing regularities, as compared to arbitrary associations. To test these hypotheses we introduce a task that requires the learning of face–location associations and later retrieval of locations based on face cues. Half of the material responds to complex associative regularities regarding the combination of facial features and locations, whereas the other half of the faces is randomly assigned to one of the remaining locations. This creates 'rule-locations': locations that have a specific type of face associated with it, and 'no-rule locations': locations that can be paired with any type of face. During encoding, the regularities associated with a given location can only be extracted across multiple face–location items that are presented interleaved with faces from other locations. This means that the build-up of hippocampus-dependent representations of individual face–location associations is a necessary step towards regularity extraction.

Memory for the location of faces is tested shortly after encoding and 48 h later, while brain activity is monitored through functional magnetic resonance imaging (fMRI). We expect that the neural networks underlying retrieval of rule-based and non-rule based items will be similar shortly after learning, but will differentiate over time, consequent to the extraction and preferential consolidation of cross-episodic regularities.

Materials and methods

Subjects

Thirty-one subjects (five males, mean age ± SD: 20.76 ± 2.71) gave written informed consent and received either course credits or a financial compensation for participation in this experiment, which was approved by the local ethics committee. Six were excluded: two for not reaching the pre-set number of trials (10) in a given condition needed for the fMRI analysis, two for expressing insufficient explicit rule knowledge as measured with an exit questionnaire,[1] one due to joystick malfunctioning during scanning and finally one based on an outlier analysis on retrieval performance (z-score < − 2.5). The final group therefore consisted of 25 subjects.

Stimuli

Seventy-two grayscale pictures of emotionally neutral faces were created using Faces™ software (IQ Biometrix, 2003). Each face had several non-critical features. However, three critical features occurred in each face: faces were either 1) young adult or aged; 2) slender or stout and had either 3) headwear (caps, hats or headbands) or no headwear. For 6 out of the 8 possible 3-way combinations of these features 12 faces were created. Each of these face categories had one unique combination of two features (e.g. headwear and slender face) that did not occur in other categories. The critical facial features could come in various forms (e.g. different types of headwear, and wrinkle patterns), contributing to the perceptual distinctiveness of the faces (see Supplementary materials Table 1, for a full description of the six face categories).

Each face was coupled to one of six screen locations in order to create face–location associations (12 faces to each location). Three locations were appointed as rule-locations, meaning that all 12 faces associated to that location belonged to the same category. The other three locations were no-rule-locations and the faces in the three remaining categories were randomly assigned to these locations. Thus, half of the associations to be learned responded to regularities governing face placements, whereas the other half did not (see Fig. 1 for an illustration of the experimental design and the Supplementary materials for an elaboration of the task rationale). Finally, the positions of the rule/no-rule locations, as well as the categories associated with the rule/no-rule locations were counterbalanced over subjects.

Procedure

Subjects were informed that the goal of the task was to learn all 72 face–location associations. They were told that for some locations they could learn rules, made up of the combinations of physical facial features, which could help them place the faces at that location. Subjects were not informed which locations or what physical features were relevant for regularity extraction. Therefore, the initial learning strategy was the same for rule and no-rule faces. The learning phase consisted of four encoding–retrieval cycles. During an encoding block, each of the 72 faces popped up over a mid-screen fixation cross and moved to one of the six locations that were organized hexagonally around the fixation cross. Immediately after each encoding block, a retrieval block followed in which subjects were instructed to indicate the correct location of each face. Subjects used a joystick to move the cursor from the fixation cross to the selected location and confirmed their choice with a button press. In the first three cycles, subjects received feedback on each placement: if the correct location was chosen, a green circle appeared at the correct location, and the face moved to that location; if an incorrect location was chosen, a red circle appeared at the incorrect location, followed by a green circle at the correct location. Subsequently, the subject had to make a movement to the correct location, after which the face moved to that location. In the fourth retrieval block, no feedback was given, but subjects had to indicate their response confidence on a five-point scale (1 = unsure to 5 = sure). A short break was given after each cycle, with a longer break (10 min) after the second cycle, during which subjects made puzzles. The order of the faces was randomized over blocks and over subjects, with the proviso that the same set of faces always appeared in either the first or the second half of each block.

Thirty minutes after the end of the learning phase, subjects entered the first fMRI session (recent condition). The second fMRI session occurred 48 h after the start of the learning phase (remote condition). During both scan sessions, subjects performed a cued recall test for face–location memory under fMRI data acquisition. All 72 faces served as cues and were presented on the fixation cross, in random order. Each face, surrounded by the six location probes, stayed on-screen for 4 s. Subjects were instructed to indicate the correct location by a

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[1] In order to make sure that the rule trials reflect trials for which subjects actually made use of rules, subjects that did not pick at least 2 out of 3 correct rule locations in the closed-format version of the rules questionnaire were excluded from the analysis.