cadherin stability. That the emergence of p120 coincides with the first fully functional classical cadherin complex, and not with the α- and β-catenin associated roles in *Dictyostelium*, suggests that p120 was originally introduced to the other catenins through physical association with the cadherins. Thus, it is possible that the *Dictyostelium* and metazoan complexes behave quite similarly with respect to the ancient collaboration between α- and β-catenins, and differ primarily by the addition of p120 and its roles in modulating cadherin function. Regardless, this new perspective on α-catenin and the extent of mechanistic similarity between the *Dictyostelium* and metazoan systems will be of interest on multiple levels to cell and evolutionary biologists alike.

References

1. Hedges, S.B. (2002). The origin and evolution of model organisms. Nat. Rev. Genet. *3*, 838–849.
2. King, N. (2004). The unicellular ancestry of animal development. Dev. Cell *7*, 313–325.
3. Shalchian-Tabrizi, K., Minge, M.A., Espelund, M., Orr, R., Ruden, T., Jakobsen, K.S., and Cavalier-Smith, T. (2008). Multigene phylogeny of choanozoa and the origin of animals. PLoS ONE *3*, e2098.
4. Dickinson, D.J., Nelson, W.J., and Weis, W.I. (2011). A polarized epithelium organized by beta- and alpha-catenin predates cadherin and metazoan origins. Science *331*, 1336–1339.
5. Drees, F., Pokutta, S., Yamada, S., Nelson, W.J., and Weis, W.I. (2005). Alpha-catenin is a molecular switch that binds E-cadherin-beta-catenin and regulates actin-filament assembly. Cell *123*, 903–915.
6. Carnahan, R.H., Rokas, A., Gaucher, E.A., and Reynolds, A.B. (2010). The molecular evolution of the p120-catenin subfamily and its functional associations. PLoS ONE *5*, e15747.

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DOI: 10.1016/j.cub.2011.04.043

Comparative Cognition: Comparing Human and Monkey Memory

Humans store a limited number of items in short-term working memory to perform subsequent operations. A newly described assessment of memory in rhesus monkeys suggests qualitative similarities and quantitative dissimilarities to humans.

Jonathon D. Crystal

The metaphor of the brain as a computer dominates our thinking about human cognition and memory [1]. The metaphor highlights the digital nature of modern computers and applies related features to the fascinating abilities that people have to remember information from the past when performing subsequent operations on that information. According to this perspective, human memory consists of discrete slots that store discrete pieces of information. How much can be remembered depends on the total number of slots available (overall capacity), the number of pieces of information arriving at any one time (selective attention), and the number of slots already filled with old information (memory load) [2,3]. Because this classic perspective of cognitive science predates many modern discoveries about the brain, we might wonder about the viability of the hypothesis that the brain has discrete slots to store discrete pieces of information. As reported in this issue of *Current Biology*, Elmore *et al.* [4] have compared the memory capacity of humans and rhesus monkeys with results that raise serious questions about this perspective.

In the new study [4], people or monkeys viewed several objects, for example, clip art icons, presented in an array (Figure 1). After a brief delay, another array of objects was presented, but one object was changed to a different item. The task for the person or monkey was to touch the changed object. Accuracy in detecting the changed object depends on the number of objects in the initially presented display. The capacity of short-term visual working memory — the number of discrete memory slots — can be estimated from the functional change in accuracy with display size. Following the assumptions of a discrete-memory model [5], Elmore *et al.* [4] estimated that monkey visual short-term working memory capacity is at most one item, whereas capacity for humans was estimated to be perhaps as large is three items.

Is it possible that people remember only three items and monkeys remember only one item? The claim that monkeys remember only one item is particularly paradoxical given the observed competency of monkeys in reporting about lists of pictures or sounds as long as four items [6]. The potential underestimate of capacity may stem from the assumptions of discrete memory slots. Indeed, when a distributed, noisy memory representation (consistent with physiological properties of the brain [7]) is assumed, the data suggest that visual short-term working memory in humans and monkeys is a continuous resource that is distributed among many objects [4]. Limitations in memory performance, according to this continuous-resource view [8,9], are a direct consequence of noise in the internal representation of each object rather than being due to a fixed capacity of discrete items.

It is remarkable that a fundamental discovery about the representation of information in humans comes from a paradox about memory in rhesus monkeys. Hence, it is valuable to reflect on the comparative origins of this discovery. The key ingredient in attempting to gain insight into human cognition from work on an animal model is the use of identical tactics — the same procedures, concepts, quantitative theories — for testing both species, as in the work of Elmore *et al.* [4]. By contrast, many studies of cognition in animals have used the same terminology [10], but the procedures, concepts, and/or quantitative theories have sometimes been strikingly disconnected from human research. Although there is the appearance of comparability, the disconnect may limit the discovery of fundamental operating characteristics of memory, which ultimately may limit the ability to translate discoveries from

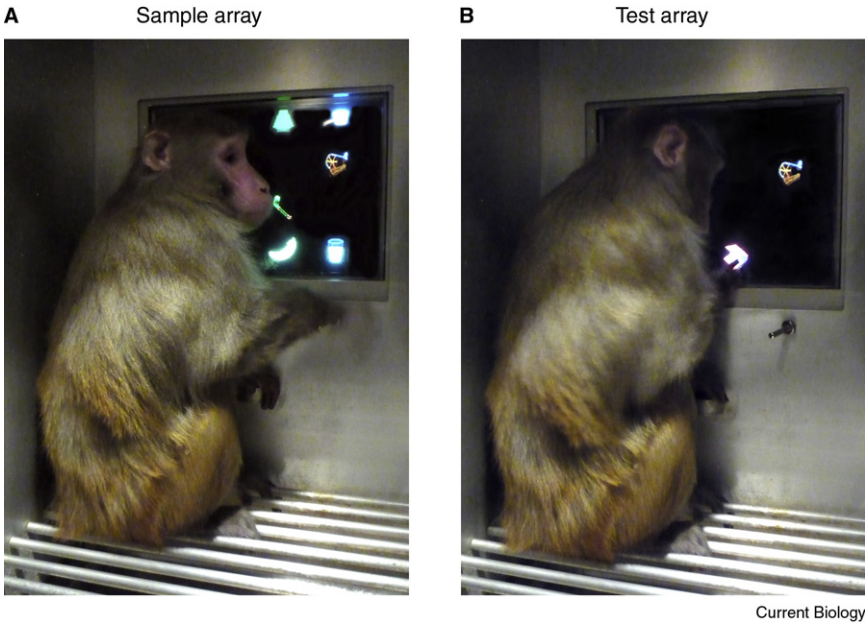

Figure 1. Change detection memory in rhesus monkeys and humans.

A monkey (A,B) or human (not shown) subject viewed a sample array (A) of clip art icons displayed on a touch-sensitive computer screen. After presentation of a sample array of six items (A) and a brief delay, a test array (B) was displayed. The test array consisted of an icon that was presented earlier in the sample array ('spinning wheel', B) and an icon that was changed (the 'envelope' in B replaced the 'banana' from A). Touching the changed item (correct response) resulted in food/drink rewards for monkeys (a drinking spout and pellet cup are below the screen at right and center, respectively, B) or a green light for people. Touching the item that had not changed (incorrect response) resulted in the absence of reward for monkeys or a red light for people. The sample display size was 2, 4, or 6 for monkeys and 2, 4, 6, 8, or 10 for people. (Photos courtesy of L. Caitlin Elmore and Anthony A. Wright.)

animal models of memory to disorders of memory in people [11,12]. Hence, one lesson to be learned from the paradox in the Elmore *et al.* [4] study is the power of identical tactics.

Another recent advance illustrates the renewed focus on identical tactics in animal and human memory. Human memory is often separately assessed using tests of recognition and recall: in recognition, the to-be-remembered material is presented amidst novel lures while you try to remember (a task that may be solved by detecting which items are familiar), whereas in recall, the to-be-remembered information is absent (which requires bringing the memory to mind through recollection). All tests of animal memory are arguably recognition tests (familiarity memory). Basile and Hampton [13] recently reported in this journal the first evidence that rhesus monkeys can recall information that was not present at the time of testing. In their demonstration, monkeys reproduced simple shapes from memory on a touchscreen, in a way that is analogous to a child's connect-the-dot game with a uniform grid of dots. They found that the memory performance of monkeys paralleled that of humans in other recall and recognition tests.

The theme of identical tactics has a broader lesson for efforts to model other types of memory from a comparative perspective. Episodic memory is memory for unique, personal past experiences that happened to you [14] and is profoundly impaired in Alzheimer's disease [15]. In the comparative study of episodic memory, progress has been made in modeling the content of episodic memories in animals [16,17]; however, these methods have not yet used identical tactics. To develop converging lines of evidence that animals have episodic memories [18,19], it will be critical to increase the mapping of methods, concepts, and quantitative measures. The use of identical tactics in studying animals and humans holds enormous potential to translate discoveries of biological properties of memory in animal preclinical models to the study of disorders of human memory. Hence, the benefit may be an increase in the ability to produce relief for people suffering from profound impairments in memory. Change-detection memory may potentially be used to study episodic memory [6,20], which would greatly enhance similarity of tactics in animal and human experiments. In a change-detection memory task, icon displays are presented sequentially, and the ability to successfully detect change is likely influenced by repeating icons from time to time, thereby promoting the development of proactive interference between an icon from a current study display and one from an old study display [6]. A significant challenge for a change-detection approach will be to implicate a role for recollection and rule out the use of familiarity-based memory processes.

References

1. Neisser, U. (1967). Cognitive Psychology (New York: Appleton-Century-Crofts).
2. Cowan, N. (2001). The magical number 4 in short-term memory: A reconsideration of mental storage capacity. Behav. Brain Sci. *24*, 87–114.
3. Cowan, N. (2005). Working Memory Capacity (New York: Psychology Press).
4. Elmore, L.C., Ma, W.J., Magnotti, J.F., Leising, K.J., Passaro, A.D., Katz, J.S., and Wright, A.A. (2011). Visual short-term memory compared in rhesus monkeys and humans. Curr. Biol. *21*, 975–979.
5. Eng, H., Chen, D., and Jiang, Y. (2005). Visual working memory for simple and complex visual stimuli. Psychonom. Bull. Rev. *12*, 1127–1133.
6. Wright, A.A. (2007). An experimental analysis of memory processing. J. Exp. Anal. Behav. *88*, 405–433.
7. Faisal, A.A., Selen, L.P.J., and Wolpert, D.M. (2008). Noise in the nervous system. Nat. Rev. Neurosci. *9*, 292–303.
8. Wilken, P., and Ma, W.J. (2004). A detection theory account of change detection. J. Vis. *4*, 1120–1135.
9. Bays, P.M., and Husain, M. (2008). Dynamic shifts of limited working memory resources in human vision. Science *321*, 851–854.
10. Honig, W.K. (1978). Studies of working memory in the pigeon. In Cognitive Processes in Animal Behavior, S.H. Hulse, H. Fowler, and W.K. Honig, eds. (Hillsdale, NJ: Erlbaum), pp. 211–248.
11. Baddeley, A. (1992). Working memory. Science *255*, 556–559.
12. Lange, K.W., Sahakian, B.J., Quinn, N.P., Marsden, C.D., and Robbins, T.W. (1995). Comparison of executive and visuospatial memory function in Huntington's disease and dementia of Alzheimer type matched for degree of dementia. J. Neurol. Neurosurg. Psychiatry *58*, 598–606.
13. Basile, B., and Hampton, R.R. (2011). Monkeys recall and reproduce simple shapes from memory. Curr. Biol *21*, 774–778.
14. Tulving, E. (1983). Elements of Episodic Memory (New York: Oxford University Press).
15. Le Moal, S., Reymann, J.M., Thomas, V., Cattenoz, C., Lieury, A., and Allain, H. (1997). Effect of normal aging and of Alzheimer's disease on episodic memory. Dement. Geriatr. Cogn. Disord. *8*, 281–287.
16. Clayton, N.S., Salwiczek, L.H., and Dickinson, A. (2007). Episodic memory. Curr. Biol. *17*, R189–R191.

17. Zhou, W., and Crystal, J.D. (2009). Evidence for remembering when events occurred in a rodent model of episodic memory. Proc. Natl. Acad. Sci. USA *106*, 9525–9529.
18. Crystal, J.D. (2009). Elements of episodic-like memory in animal models. Behav. Process. *80*, 269–277.
19. Crystal, J.D. (2010). Episodic-like memory in animals. Behav. Brain Res. *215*, 235–243.
20. Wright, A.A., Katz, J.S., Magnotti, J., Elmore, L.C., Babb, S., and Alwin, S. (2010). Testing pigeon memory in a change detection task. Psychonom. Bull. Rev. *17*, 243–249.

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DOI: 10.1016/j.cub.2011.04.027

Primary Cilia: How to Keep the Riff-Raff in the Plasma Membrane

A recent report suggests that plasma membrane proteins are excluded from primary cilia via anchoring to the cortical actin cytoskeleton. These findings challenge the existence of a diffusion barrier at the base of the cilium.

David K. Breslow and Maxence V. Nachury

The primary cilium is a microtubule-based organelle that exposes cell-surface receptors and concentrates signaling components [1]. The diversity of signaling pathways organized by cilia is evidenced by the variety of symptoms — e.g. sensory defects, skeletal dysplasia, kidney cysts, and obesity — resulting from ciliary dysfunction. Remarkably, primary cilia are able to concentrate signaling proteins despite the considerable problem posed by the topological continuity of the plasma and ciliary membranes. Here, lateral diffusion would predict that lipids and membrane proteins should equilibrate between these compartments, yet the ciliary and plasma membranes are known to contain distinct lipids and proteins.

How then do cilia establish and maintain the unique complement of proteins and lipids required to organize signal transduction? Previous studies have indicated that a physical barrier blocks lateral diffusion into and out of cilia and that ciliary proteins contain signals that enable them to cross this barrier, either by vesicular trafficking or by lateral transport from the plasma membrane [2,3]. But are there also mechanisms to prevent plasma membrane proteins from entering cilia? A recent report from the laboratory of Ira Mellman now suggests that tethering of plasma membrane proteins to the actin cytoskeleton, rather than a diffusion barrier, serves to exclude proteins from cilia [4].

These authors followed Madin-Darby canine kidney (MDCK) cells through apicobasal polarization and ciliogenesis, focusing on podocalyxin/gp135 (PODXL), a transmembrane protein localized across the apical surface but excluded from a region of the apical membrane at the base of the cilium [5]. The exclusion of proteins such as PODXL from this periciliary membrane domain (PCMD) had been previously cited as evidence for the existence of a periciliary diffusion barrier encircling the PCMD [2,6]. Nonetheless, PODXL was also known to be anchored to the cortical actin cytoskeleton via binding of its PDZ interaction motif to NHERF proteins. It is this network of protein interactions that Francis *et al.* [4] have found to be required for exclusion of PODXL from the PCMD (Figure 1A). Mutation of PODXL's PDZ motif or depletion of NHERF1 allows PODXL to enter the PCMD and increases its lateral mobility (Figure 1B). Conversely, grafting this PDZ motif (or other actin-tethering elements) onto proteins that can normally access the PCMD is sufficient to exclude them from this region of the apical membrane and decrease their mobility.

Interestingly, mutation of the PDZ domain of PODXL not only allows it to enter the PCMD, but also to enter the primary cilium, casting doubt on the existence of a diffusion barrier at the base of cilia that excludes PODXL. Furthermore, Francis *et al.* [4] find that glycosylphosphatidylinositol-anchored GFP, a marker whose apparent exclusion from cilia has been cited as evidence for a diffusion barrier [6,7], does in fact localize to cilia in live cells. This discrepancy is attributed to fixation artifacts and indicates that live imaging is critical for studies of ciliary localization. However, caution must also be exercised when expressing exogenous proteins because the cytoskeletal anchoring mechanism is saturable and subject to overexpression artifacts. On the basis of these results, Francis *et al.* [4] propose that there is no strict diffusion barrier at the base of cilia and that plasma membrane proteins are instead excluded from the PCMD and cilium by an actin-linked network of protein–protein interactions (Figure 1A). Furthermore, Francis *et al.* [4] provide evidence that ciliary enrichment in the absence of restricted diffusion may be enabled by analogous tethering to axonemal microtubules.

The work of Francis *et al.* [4] raises important questions regarding the partitioning of membrane proteins between the ciliary and plasma membranes, especially in light of previous data indicating that primary cilia do possess a diffusion barrier. Specifically, Hu *et al.* [7] used fluorescence recovery after photobleaching (FRAP) to show that ciliary membrane proteins are highly mobile within cilia and within the plasma membrane but are not able to diffuse readily between these compartments. Additionally, several groups [6,8,9] have reported that the ciliary membrane is enriched in specific lipids. How the lipid content of ciliary and plasma membranes is prevented from equilibrating is not known, but a diffusion barrier is an appealing and plausible mechanism.

If there is a ciliary diffusion barrier, what might be its molecular basis? One candidate is septins, which Hu *et al.* [7] recently found to localize at the base of cilia and to limit diffusion of membrane proteins into cilia. Alternatively, diffusion could be restricted by increased membrane order [6] or high curvature at the base of cilia, as is especially apparent in cilia with a prominent ciliary pocket [10]. Yet another possibility is suggested from studies on the diffusion barrier that separates the