Neural basis of memory (2): multiple memory systems

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Monday 12, 19, 26 Jan; 2, 9, 23 Feb 2004; 10 am
Physiology Main Lecture Theatre
Slides will be at pobox.com/~rudolf/psychology
Rhinal cortex
Medial temporal lobe lesions and DNMTS

Murray & Mishkin (1998)
TE (part of inferotemporal cortex) and perirhinal cortex

Murray & Bussey (1999)
Perirhinal cortex is the first polymodal ventral stream area

Murray & Bussey (1999)
Double dissociation of TE and perirhinal lesions

CON = control
MTG = dorsal TE, in inferotemporal cortex
PRh = perirhinal cortex

Buckley et al. (1997)
‘Odd one out’: perirhinal cortex and visual discrimination (1)

Buckley et al. (2001)
‘Odd one out’: perirhinal cortex and visual discrimination (2)

Some tasks: fine (even if tasks are difficult)

Others: impaired. Why?

Buckley et al. (2001)
Perirhinal cortex: feature conjunctions (resolving ambiguity)

Bussey & Saksida (2002)
Perirhinal cortex: feature conjunctions (resolving ambiguity) 2

Monkeys

Bussey et al. (2002)
Semantic memory
Perinatal hypoxia: impaired episodic, preserved semantic memory.

Gadian et al. (2000)

### Table 1 Results of neuropsychological tests

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Mean ± SD</th>
<th>Normal subjects (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at testing (years)</td>
<td>12.8</td>
<td>11.7</td>
<td>11.6</td>
<td>16.3</td>
<td>12.3</td>
<td>12.9 ± 1.9</td>
<td>13.6 ± 1.3</td>
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<tr>
<td>Digit span</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Forward</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>7</td>
<td>6.8 ± 0.8</td>
<td>6.4 ± 1.2</td>
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<tr>
<td>Backward</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>4.7 ± 1.3</td>
<td>4.2 ± 1.5</td>
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<tr>
<td>Literacy (WORD) subtests</td>
<td></td>
<td></td>
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<tr>
<td>Basic reading (standard score)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual score</td>
<td>85</td>
<td>97</td>
<td>99</td>
<td>102</td>
<td>105</td>
<td>97.6 ± 7.7</td>
<td>100 ± 15</td>
</tr>
<tr>
<td>IQ predicted score</td>
<td>83</td>
<td>86</td>
<td>89</td>
<td>106</td>
<td>92</td>
<td>91.2 ± 8.9</td>
<td></td>
</tr>
<tr>
<td>Spelling (standard score)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Actual score</td>
<td>77</td>
<td>96</td>
<td>88</td>
<td>84</td>
<td>118</td>
<td>92.6 ± 15.8</td>
<td>100 ± 15</td>
</tr>
<tr>
<td>IQ predicted score</td>
<td>85</td>
<td>88</td>
<td>90</td>
<td>105</td>
<td>93</td>
<td>92.2 ± 7.7</td>
<td></td>
</tr>
<tr>
<td>Reading comprehension (standard score)</td>
<td></td>
<td></td>
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<tr>
<td>Actual score</td>
<td>84</td>
<td>87</td>
<td>74</td>
<td>97</td>
<td>87</td>
<td>85.8 ± 8.2</td>
<td>100 ± 15</td>
</tr>
<tr>
<td>IQ predicted score</td>
<td>81</td>
<td>85</td>
<td>87</td>
<td>107</td>
<td>91</td>
<td>90.2 ± 10.1</td>
<td></td>
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<tr>
<td>VIQ subtests</td>
<td></td>
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<tr>
<td>Information</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>8.6 ± 1.1</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>11</td>
<td>9</td>
<td>8.4 ± 1.7</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>Comprehension</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>14</td>
<td>8</td>
<td>9.2 ± 2.8</td>
<td>10 ± 3</td>
</tr>
</tbody>
</table>

### Table 2 Results of tests of memory function

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Mean ± SD</th>
<th>Normal subjects (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Story recall (Immediate)</td>
<td>25.0</td>
<td>38.9</td>
<td>20.8</td>
<td>27.2</td>
<td>11.3</td>
<td>24.6 ± 10.0</td>
<td>41.4 ± 14.9</td>
</tr>
<tr>
<td>(Delayed)</td>
<td>2.2</td>
<td>2.8</td>
<td>0</td>
<td>3.5</td>
<td>3.4</td>
<td>2.4 ± 1.4</td>
<td>32.3 ± 15.4</td>
</tr>
<tr>
<td>Geometric design (Immediate)</td>
<td>53.6</td>
<td>32.1</td>
<td>57.1</td>
<td>64.2</td>
<td>35.7</td>
<td>48.5 ± 14.0</td>
<td>82.2 ± 13.5</td>
</tr>
<tr>
<td>(Delayed)</td>
<td>14.3</td>
<td>14.3</td>
<td>0</td>
<td>3.6</td>
<td>10.7</td>
<td>10.7 ± 5.0</td>
<td>77.8 ± 16.9</td>
</tr>
<tr>
<td>Children’s Auditory Verbal Learning Test (Immediate memory span)</td>
<td>105</td>
<td>82</td>
<td>89</td>
<td>109</td>
<td>74</td>
<td>91.8 ± 14.9</td>
<td>100 ± 15.0</td>
</tr>
<tr>
<td>(Delayed)</td>
<td>60</td>
<td>60</td>
<td>61</td>
<td>63</td>
<td>60</td>
<td>60.8 ± 1.3</td>
<td>100 ± 15.0</td>
</tr>
</tbody>
</table>

Gadian et al. (2000)
**Semantic dementia: impaired semantic, preserved episodic?**

1. **Semantic task** — name a familiar object

2. **Episodic task** — recognize an object (‘perceptually identical’)

3. **Mixed task** — recognize a different example of an object (‘perceptually different’)

*Graham et al. (2000)*
Semantic dementia: impaired semantic, preserved episodic? 2

Graham et al. (2000)

**impaired semantic performance**

**normal object recognition;**
failure to recognize a different example of the same kind of object
Semantic dementia: damage to a simple associative net?

Moss et al. (2002)
Consolidation: hippocampal–cortical interactions?
Retrograde amnesia: hippocampus / medial temporal lobe

![Graph showing recall over time](image)

**Figure 14.9.** Recall of information from the patient’s [P.Z.] published autobiography [Butters and Cermak, 1986].

**Gradual transfer of memories from hippocampus (or MTL) to cortex elsewhere?**

*Scoville & Milner (1957); Squire et al. (2001)*
Alternative: the ‘multiple memory trace’ model

- This suggests that the hippocampus is ALWAYS important for certain types of memory, especially autobiographical memory.
- Memories are ‘laid down’ in both hippocampus and neocortex elsewhere.
- Repeated/rehearsed memories have multiple traces.
- For some kinds of memory (e.g. semantic), older memories have more cortical traces that can be used for retrieval. For these memories, hippocampal lesions can lead to temporally-graded retrograde amnesia (older memories survive better).
- However, autobiographical and other ‘context’-dependent memories always require the hippocampal system (‘contextual index’) for retrieval.

_Nadel & Moscovitch (1997)_

**Patient VC:** seizures (associated with a tachyarrhythmia), subsequently amnesic. MRI: hippocampal atrophy, sparing of adjacent cortex. **Flat** retrograde amnesia.

_Cipolotti et al. (2001)_

![Graph](image)  
Fig. 6. Results on the famous public events questionnaire test.
Temporally-graded activation (1)

Haist et al. (2001)
Temporally-graded activation (2)

Haist et al. (2001)
Prospective animal studies of retrograde amnesia

CON = control
H = hippocampus
EC = entorhinal cortex
FX = fornix

from Squire et al. (2001)
Hippocampal-cortical consolidation (1)
Hippocampal-cortical consolidation (2)
Hippocampal-cortical consolidation (3)
Hippocampal-cortical consolidation (4)
Does blockade of NMDA receptors prevent forgetting?

Systemic CPP (black circles) blocks decay of hippocampal LTP, compared to vehicle (white circles).

Systemic CPP (black circles) blocks decay of a memory for 8-arm radial maze performance, a task that is hippocampus-dependent, compared to vehicle (white triangles).

Villarreal et al. (2001)
The stability–plasticity dilemma: catastrophic interference

Rosenzweig et al. (2002), after an idea by Grossberg (1982)
Sleep and consolidation
'Replay' of hippocampal activity during sleep

Figure 3. Example Correspondence between a REM Template and RUN Activity
(Top) Rasters of 10 pyramidal cells during a 75 s window from RUN. The RUN time axis is scaled to maximize raster alignment with REM (SF = 1.6). (Bottom) Rasters of the same cells over the duration of a 120 s REM template.

Louie & Wilson (2001)
Subject must fixate centre and detect orientation of the /// pattern.
Performance doesn’t improve until several hours after practice.
Improvements are specific to the trained quadrant (and eye), and last for years, suggesting alterations in early visual processing.
‘Procedural’ memory consolidation and sleep (2)

Stickgold et al. (2002). Between-subjects design (subjects were tested only once).
Fischer et al. (2002). “Sleep forms memory for finger skills.”
REM sleep across species

**High REM Sleep**
> 3 hours of REM sleep/day

- Platypus
  *Ornithorhynchus anatinus*
  - 8 REM, 14 Total
- Thick-tailed Opossum
  *Lutreolina crassicaudata*
  - 6.6 REM, 18 Total
- Big Brown Bat
  *Eptesicus fuscus*
  - 3.9 REM, 19.7 Total
- European Hedgehog
  *Erinaceus europaeus*
  - 3.5 REM, 10.1 Total
- Ferret
  *Mustela nigripes*
  - 6 REM, 14.5 Total
- Armadillo
  *Dasypus novemcinctus*
  - 3 REM, 17 Total

**Human**
*Homo sapiens*
- 2 REM, 8 Total

**Low REM Sleep**
≤ 1 hour of REM sleep/day

- Guinea Pig
  *Cavia porcellus*
  - 1 REM, 9.5 Total
- Sheep
  *Ovis aries*
  - 0.6 REM, 5.9 Total
- Giraffe
  *Giraffa camelopardalis*
  - 0.5 REM, 4.5 Total
- Bottlenose Dolphin
  *Tursiops truncatus*
  - <0.2 REM, 10 Total

- Guinea Baboon
  *Papio papio*
  - 1 REM, 9.5 Total
- Horse
  *Equus caballus*
  - 0.5 REM, 3 Total

*Siegel (2001)*
‘Sleep inspires insight.’ (1)

“Eventually – by about 1864 – I was back at my research. It was at this time that I had my second famous dream... I turned my chair to the fire and dozed.

Again the atoms were gamboling before my eyes... My mental eye... could now distinguish larger structures of manifold conformation; long rows sometimes more closely fitted together all twining and twisting in snake-like motion. But look! What was that? One of the snakes had seized hold of its own tail, and the form whirled mockingly before my eyes.

As if by a flash of lightning I awoke; and... spent the rest of the night in working out the consequences of the hypothesis.”

Kekulé (1829–1896), organic chemist. However, his work depended heavily on the work of Couper and Loschmidt, and it has been suggested that Kekulé made up the dream story to distract from this!
‘Sleep inspires insight.’ (2)

Reconsolidation
‘Reconsolidation’

consolidation

Short-term memory (STM)  | Long-term memory (LTM)
• Lasts for seconds to hours  | • Lasts for days to weeks
• ‘Labile’ (sensitive to disruption)  | • Consolidated (insensitive to disruption)
• Does not require new RNA or protein synthesis  | • Does require new RNA or protein synthesis

reconsolidation

Active state (AS)  | Inactive state (IS)
• Lasts for seconds to hours  | • Lasts for days to weeks
• ‘Labile’ (sensitive to disruption)  | • Inactive (insensitive to disruption)
(Does not require new RNA or protein synthesis)  | (Does require new RNA or protein synthesis)

Nader (2003)
Reconsolidation in the amygdala (1)

Conditioned freezing requires the basolateral amygdala (BLA) — the BLA is a key site of association.

- **Train CS(tone) → US(shock)**
- **Present CS; infuse anisomycin (protein synthesis inhibitor) or vehicle into BLA**
- **Test conditioned freezing to the CS**

*Nader et al. (2000)*
Reconsolidation in the amygdala (2)

Nader et al. (2000)
Reconsolidation in the amygdala (3)

Figure 3 Intact memory if anisomycin infusions are delayed by 6 h. 

a, The behavioural procedure used for experiment 2. Vertical open-headed arrows represent infusions.

b, Freezing on test 1 was specific to the CS and comparable across groups.

c, Percent freezing during test 2. The groups are not significantly different. All data points represent group means ± s.e.m.

Nader et al. (2000)
Reconsolidation in the amygdala (4)

Figure 4 Fourteen days after training, anisomycin infusions after reactivation of the memory still produce amnesia. a, The behavioural procedure used for experiment 3. Vertical open-headed arrows represent infusions. b, Freezing during test 1 was specific to the CS and was comparable across groups. c, Percent freezing on test 2. All data points represent group means ± s.e.m.

Nader et al. (2000)
‘Cellular’ and ‘systems’ reconsolidation in the hippocampus

- Train CS (context) → US (shock)
- Present CS (or not); lesion hippocampus (or not).
- Test conditioned freezing to the CS

Debiec et al. (2002)
Patients with OCD or hallucinations were given ECT after being prompted to act out their desires or after their hallucination had begun. All 28 patients... improved dramatically for periods ranging from 3 months to the time of publication of the manuscript, 10 years later. One relapsed, but was treated once using the same approach and recovered.

Many of the subjects had previously received between 5 and 28 ECT sessions, while anaesthetized, with little benefit.

Case study. 30-year-old woman with OCD received 22 ECT treatments in 1 year while anaesthetized, but became worse. She was made to act out her compulsion of killing her mother with a butcher’s knife and was then administered a single session of ECT while still awake. ‘The next day, greatly improved, she went home and spoke kindly to her mother for the first time in years. She asked her mother “Do you love me?” and then kissed her. When the author asked if she still felt like stabbing her mother, she laughed and said, “Oh, she doesn’t deserve anything like that”’. She returned home and to work, and remained free of symptoms for the 2 years up to the publication of the study.

Rubin et al. (1969); Rubin (1976); see Nader (2003)
Cautionary note…

• There’s a long history of research into the effects of protein synthesis inhibitors on memory (Flexner et al., 1963).

• Protein synthesis inhibitors have side-effects. Might these be responsible for effects on consolidation — or interfere with retrieval of the memory?

• The original work foundered because the amnesic effects of puromycin (a protein synthesis inhibitor) were not duplicated by another protein synthesis inhibitor; it turned out that a metabolite of puromycin was responsible for its effects (by an unknown mechanism) (Flexner et al. 1967).

*Those who cannot remember the past are condemned to repeat it.*

George Santayana, 1863–1952
Amnesia... a problem with retrieval?

Graf et al. (1984)  

Warrington & Weiskrantz (1970)
‘Loss’ of new or reactivated memories following hypothermia

- Passive avoidance task (black chamber → shock; measure latency to re-enter black chamber). So high latency = good memory.
- Hypothermia (21 °C) to induce amnesia.
- ‘Cue reminder’ = putting the animals back in the black chamber briefly (no shock).

‘Newly acquired’: training → hypothermia

‘Old, cue reactivated’: training → cue reminder → hypothermia

‘Old, no reactivation’: training → ... → hypothermia

Mactutus et al. (1982), experiment 1
Interfering with reconsolidation… or a problem with retrieval?

- Remember, high latency = good memory.

‘Newly acquired’ group: training → hypothermia.
‘Cue reactivated’ group: training → … → cue reminder → hypothermia.
All groups then receive additional ‘reminder’ hypothermia, or not.

\[\text{black} = \text{reminder hypothermia} \]
\[\text{white} = \text{no reminder}\]

Mactutus et al. (1982), experiment 6
“Common to the amnesias for both new and old learning is a striking persistence of the original information.”

Mactutus et al. (1982)
Habit learning
Habits and learning theory

Adams (1982)
A double dissociation between PD and amnesiacs (1)

Task 1 (probabilistic classification): one to three cards are shown. The subject must predict sunshine or rain. Feedback is provided (correct/incorrect). One cue is associated with sunshine on 25% of occasions; one on 43% of occasions; one 57%; one 75%.

Task 2 (declarative): memory for features of the game (screen layout, cues, etc.) is tested with four-way multiple-choice questions.

Knowlton et al. (1996)
A double dissociation between PD and amnesiacs (2)

- **PD patients**: impaired on probabilistic classification task, not declarative. (PD* = severe.)
- **Amnesic patients** (with bilateral hippocampal damage or midline diencephalic damage): impaired on declarative task, not probabilistic classification.

_Knowlton et al. (1996)_
Habits and the dorsal striatum (1)

Packard & McGaugh (1996)
Habits and the dorsal striatum (2)

Packard & McGaugh (1996)
Habits and the dorsal striatum (3)
