Brain Mechanisms of Memory and Cognition – 5

Neural basis of memory (2): multiple memory systems

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Department of Experimental Psychology

Monday 13, 20, 27 Jan; 3, 10, 24 Feb 2003; 10 am
Physiology Main Lecture Theatre
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

**Color discrimination**

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

**DNMS**

- **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

Errors to Criterion

- Control
- PRh

Degree of Feature Ambiguity

Minimum  Intermediate  Maximum

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

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</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>
</tr>
<tr>
<td>Digit span</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Literacy (WORD) subtests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>100 ± 15†</td>
</tr>
<tr>
<td>Spelling (standard score)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<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>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<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>
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</tbody>
</table>

### VIQ subtests

<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</th>
</tr>
</thead>
<tbody>
<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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Story recall* (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>
</tbody>
</table>

Geometric design ‡ (± %)

<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</th>
</tr>
</thead>
<tbody>
<tr>
<td>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>
</tbody>
</table>

Children’s Auditory Verbal Learning Test ‡ (%)  

<table>
<thead>
<tr>
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<th>Case 4</th>
<th>Case 5</th>
<th>Mean ± SD</th>
<th>Normal subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>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>

normal digit span, vocabulary, verbal information, and verbal comprehension

severe delay-dependent impairment
**Semantic dementia: impaired semantic, preserved episodic?**

*Graham et al. (2000)*

**semantic task** — name a familiar object

**episodic task** — recognize an object (‘perceptually identical’)

**mixed task** — recognize a different example of an object (‘perceptually different’)

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

impaired semantic performance

normal object recognition;
failure to recognize a different example of the same kind of object

Graham et al. (2000)
Semantic dementia: damage to a simple associative net?

Moss et al. (2002)

Computational model

Patient with progressive semantic dementia

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

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)

Fig. 6. Results on the famous public events questionnaire test.
Temporally-graded activation

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

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

from Squire et al. (2001)
Hippocampal-cortical consolidation (1)
Hippocampal-cortical consolidation (2)
Hippocampal-cortical consolidation (3)
Hippocampal-cortical consolidation (4)
The hippocampus encodes, retrieves, consolidates (1)

Riedel et al. (1999)
The hippocampus encodes, retrieves, consolidates (2)

Riedel et al. (1999)
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.

Karni & Sagi (1991); Stickgold et al. (2002)
Procedural memory consolidation and sleep (2)

between-subjects design (subjects were tested only once).

Red = no sleep
Green = sleep
Blue = sleep

Improvement correlated with sleep type

Stickgold et al. (2002).
Procedural memory consolidation and sleep (3)

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
- Ferret *Mustela nigripes*
  - 6 REM, 14.5 Total
- Big Brown Bat *Eptesicus fuscus*
  - 3.9 REM, 19.7 Total
- European Hedgehog *Erinaceus europaeus*
  - 3.5 REM, 10.1 Total
- Armadillo *Dasypus novemcinctus*
  - 3 REM, 17 Total

**Low REM Sleep**
- < 1 hour of REM sleep/day
- Human *Homo sapiens*
  - 2 REM, 8 Total
- Guinea Pig *Cavia porcellus*
  - 1 REM, 9.5 Total
- Guinea Baboon *Papio papio*
  - 1 REM, 9.5 Total
- Sheep *Ovis aries*
  - 0.6 REM, 5.9 Total
- Horse *Equus caballus*
  - 0.5 REM, 3 Total
- Giraffe *Giraffa camelopardalis*
  - 0.5 REM, 4.5 Total
- Bottlenose Dolphin *Tursiops truncatus*
  - <0.2 REM, 10 Total

*Siegel (2001)*
Reconsolidation
### Reconsolidation

#### Consolidation

<table>
<thead>
<tr>
<th>Short-term memory (STM)</th>
<th>Long-term memory (LTM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasts for seconds to hours</td>
<td>Lasts for days to weeks</td>
</tr>
<tr>
<td>‘Labile’ (sensitive to disruption)</td>
<td>Consolidated (insensitive to disruption)</td>
</tr>
<tr>
<td>Does not require new RNA or protein synthesis</td>
<td>Does require new RNA or protein synthesis</td>
</tr>
</tbody>
</table>

#### Reconsolidation

<table>
<thead>
<tr>
<th>Active state (AS)</th>
<th>Inactive state (IS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasts for seconds to hours</td>
<td>Lasts for days to weeks</td>
</tr>
<tr>
<td>‘Labile’ (sensitive to disruption)</td>
<td>Inactive (insensitive to disruption)</td>
</tr>
<tr>
<td>(Does not require new RNA or protein synthesis)</td>
<td>(Does require new RNA or protein synthesis)</td>
</tr>
</tbody>
</table>

*Source: 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

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?

| ABSENT | ABS________ |
| INCOME | INC________ |
| FILLY  | FIL________ |
| DISCUSS| DIS________ |
| CHEESE | CHE________ |
| ELEMENT| ELE________ |

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.

black = reminder hypothermia
white = 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)