The alcoholic Korsakoff Syndrome: clinical, neuropsychological & neuroimaging aspects.

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Clinical aspects of the Korsakoff syndrome.
THE AMNESIC SYNDROME

“An abnormal mental state in which memory and learning are affected out of all proportion to other cognitive functions in an otherwise alert and responsive patient.”

VICTOR, COLLINS and ADAMS, 1971
WERNICKE-KORSAKOFF SYNDROME

WERNICKE’S ENCEPHALOPATHY:

- Ophalmoplegia
- Nystagmus
- Ataxia
- Confusion

± Peripheral Neuropathy

Differentiate: Delirium Tremens

KORSAKOFF’S SYNDROME:

“An abnormal mental state in which memory and learning are affected out of all proportion to other cognitive functions in an otherwise alert and responsive patient,” resulting from nutritional depletion i.e. thiamine depletion.
"At first, during conversation with such a patient . . . (he or she) gives the impression of a person in complete possession of his (or her) faculties; he (she) reasons about everything perfectly well, draws correct deductions from given premises, makes witty remarks, plays chess or a game of cards, in a word comports himself (herself) as a mentally sound person."

However,

"the patient constantly asks the same questions and repeats the same stories . . . may read the same page over and again sometimes for hours . . . is unable to remember those persons whom he (she) met only during the illness, for example, the attending physician or nurse".
**KORSAKOFF, 1889, on Retrograde Amnesia**

- “The disorder of memory manifests itself in an extraordinarily peculiar amnesia, in which the memory of recent events, those which just happened, is chiefly disturbed ….”

In other (cases), even the memory of remote events may also be disturbed ….

In very severe cases, the amnesia is much more profound; here, not only memory of recent events is lost, but also that of the long past …

Thus, they may believe themselves to be in the setting (or circumstances) in which they were some 30 years ago, and mistake persons … around them now for people … at that time.”
Korsakoff (1889) on Confabulation:

Confusion of “old recollections with present impressions.”

Eg:
“In telling of something about the past, the patient would suddenly confuse events and would introduce the events related to one period into the story about another period…

Telling of a trip she had made to Finland before her illness and describing her voyage in fair detail, the patient mixed into the story her recollections of Crimea, and so it turned out that in Finland people always eat lamb and the inhabitants are Tartars.”

**KORSAKOFF’S SYNDROME**

*Initial manifestations can vary:*

1. Coma, confusion → Physicians  
   *(Wallis et al, Torvik et al)*

2. *Classical Wernicke Syndrome* → Neurologists  
   *(Victor et al)*

3. Insidious → Psychiatrists, Clinical Psychologists  
   *(Moll, Cutting)*

4. Autopsy → Neuropathologists  
   *(Harper, Torvik et al)*
Autopsy studies of Wernicke-Korsakoff syndrome:

- Loss of neurons, gliosis, micro-haemorrhages in peri-ventricular and para-aqueductal brain regions.
- Cortical atrophy, esp frontally.
- Loss of large neurons in superior frontal cortex, hypothalamus and cerebellum.
- Loss of prefrontal white matter.
- Neuronal dendritic shrinkage.

What are the critical lesion sites for anterograde memory damage in the Korsakoff Syndrome?

   - 24 patients with lesions in *dorso-medial thalamic N*---Korsakoff syndrome
   - 5 patients with mammillary lesions only --- Wernicke syndrome only.

2. Thalamic lesions with mammillary sparing in trauma, tumour, infarction → amnesia

   - 2 Korsakoff patients in each study with lesions confined to *mammillary bodies, mammillo-thalamic tract and anterior thalamus* only.

   - *Anterior lesions in thalamic infarction* critical for memory disruption (C.T. scan study).

5. Harding et al (2000): damage to *anterior (principal) thalamic nuclei* critical:
   - comparison of 5 ‘Wernicke only’ vs. 8 Korsakoff cases.
### Candidate Genes

<table>
<thead>
<tr>
<th>Candidate Genes</th>
<th>Literature</th>
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<tbody>
<tr>
<td>Transketolase</td>
<td>McCool et al., 1993; Martin et al., 1995; Guerrini and Thomson, 2008</td>
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<tr>
<td>Apoe epsilon 4</td>
<td>Muramatsu et al., 1997</td>
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<tr>
<td>GABAAbeta2 &amp; GABAAalpha6 receptors</td>
<td>Loh et al., 1999</td>
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<td>ADH2<em>1/2</em>1 genotype</td>
<td>Matsushita et al., 2000</td>
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<td>DLST gene</td>
<td>Matsushita et al., 2001</td>
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<tr>
<td>SLC19A2</td>
<td>Guerrini et al., 2005</td>
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<tr>
<td>SLC19A3</td>
<td>Guerrini and Thomson, 2008</td>
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<tr>
<td>OGDH (E1K)</td>
<td>Guerrini and Thomson, 2008</td>
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Fig. 1. Summary of candidate genes implicated in the genetic susceptibility to develop WKS.
Prognosis, treatment and management:

- Acute treatment: management of Wernicke’s encephalopathy
  - high dose multi-vitamins (Pabrinex); management of delirium.
- Few follow-up studies.
- Longer-term rehabilitation: often poor facilities in the U.K.
  - contrast Netherlands
Dutch rehabilitation hostels for Korsakoff patients and alcohol-induced brain damage:

6) Wonen
Dit programma is gericht op cliënten die permanent aangewezen blijven op volledige begeleiding en verzorging. De afdeling voor woonbegeleiding bestaat uit 17 bedden. Naast een duidelijke dagstructuur is er een ruim aanbod aan activiteitenbegeleiding.

7) Begeleid Wonen (in de wijk)
Dit programma is gericht op cliënten die aangewezen zijn op beperkte begeleiding en verzorging maar niet zelfstandig kunnen wonen. Er zijn 6 plaatsen binnen 2 woningen in de wijk. Het bieden van dagstructuur en activering is hier van belang.

8) Deeltijdbehandeling
De deeltijdbehandeling is gericht op cliënten die wel al in de maatschappij kunnen functioneren, maar nog gedeeltelijke ondersteuning en oefening nodig hebben. De behandeling biedt trainingen en begeleiding hoe om te gaan met de verslaving en de geheugenproblemen.

Nazorg

Na behandeling is het vaak belangrijk dat de cliënt nog enige tijd ondersteuning krijgt. Deze nazorg kan geschieden door ver- wijzing naar een andere instantie, zoals RAGG, de ambulante verslavingszorg, Beschermende Woonvormen of Pensionshuizen. Cliënten die aangewezen blijven op klinische zorg, melden wij aan voor terugplaatsing in de regio van herkomst. U wordt tijdelijk op de hoogte gehouden van het ontslag van uw cliënt.

Consulten

De behandelaars van de Korsakov Kliniek stellen hun specialistische kennis en ervaring ook ter beschikking aan hulpverleners die elders cliënten met het syndroom van Korsakov behandelen en hierover advies of consult wensen.
Neuropsychological aspects of the Korsakoff syndrome
**PRIMARY/ ‘SHORT-TERM’/ WORKING MEMORY**
Memories lasting a few seconds or as long as rehearsed

William James - the ‘specious present’.

*Preserved in the amnesic syndrome.*

**AUTOBIOGRAPHICAL / EPISODIC MEMORY**
A person’s recollection of past incidents and events, which occurred at a specific time and place. (Can ‘travel back mentally in time’).

*Severely impaired in amnesia.*

**SEMANTIC MEMORY**
Knowledge of language, concepts, and facts which do not have a specific time or location in place.

*Variably affected in amnesia.*

**IMPlicit MEMORY**
Learning without awareness:

- Procedural (perceptuo-motor) learning (skills).

*Spared in amnesia.*
Definitions Of Memory Disorder:

- **Anterograde amnesia (A.A.)** = impairment in new learning i.e. in recall and recognition memory for episodes and facts arising after the onset of an illness or injury.

- **Retrograde amnesia (R.A.)** = loss of memory for episodes or facts which occurred before the onset of an illness or injury.
Short-term forgetting (‘the specious present’):

Words

Non-words: Corsi blocks
Forgetting rates on tests of recall memory (a failure of memory ‘consolidation’):

1. Differences in recall memory between 20 sec & 10-20 mins:

D’s= patients with diencephalic pathology (Korsakoff patients).
MTs= p’s with medial temporal pathology.
Retrograde Amnesia:

Ribot’s Law

“The progressive destruction of memory follows a logical order – a law…it begins with the most recent recollections which, being …rarely repeated and … having no permanent associations, represent organisation in its feeblest form.”

T. Ribot (1882)
RETROGRADE AMNESIA: Temporal (‘Ribot’) gradients across different remote memory tasks

Autobiographical incident recall.

Personal semantic fact recall.

News event recall.

Kopelman, 1989
Neuroimaging findings
DIENCEPHALIC AMNESIA: Korsakoff with thalamic infarct:

Memory Circuits:
Fig. 1. CT and MR images of an acute 35-year-old man with schizophrenia and acute nutritional deficiency-induced WE. (A) Axial CT at the level of the lateral ventricles. (B–E) Axial MR images at a similar level to the CT. (B) A proton density-weighted image. (C) A T2-weighted late-echo fast spin echo (FSE) image. (D) A fluid-attenuated inversion recovery (FLAIR) image. (E) A diffusion-weighted image (DWI). Note the hyperintensity of the fornix and thalamus, especially in D and E, less so in C, and lack of lesion conspicuity in A and B.

Fig. 2. Three contiguous FLAIR images (5 mm thick with a 2.5 mm skip) of the acute WE case in Fig. 1. Note the hyperintense signal in the mammillary bodies and colliculi (left), periventricular gray matter (middle), and fornix and thalamus (right).
Fig. 4. T1-weighted SPoiled GRadient echo (SPGR) images of the healthy (left panel) and WKS (right panel) men in Fig. 3. Note the shrunken mamillary bodies (arrows) in the WKS (B and D) compared with the control (A and C).
Fig. 3. Surface rendered brains (top) and rendered ventricular system (bottom, green) of a 59-year-old healthy man (A and C) and a 53-year-old man with WKS (B and D). Note the shrinking of the cortical gyri and widening of the sulci (B) and expansion of the ventricles (D) of the WKS compared with the control.

Quantification of regional atrophy in Korsakoff p’s and other alcoholics: Sullivan and Pfefferbaum, 2009
Colchester, Kingsley, Kopelman et al, 2001: Whole brain (supratentorial) segmentation:

Colchester et al., 2001
Thalamic boundaries (proton density):
Hippocampus

Parahippocampal Gyrus and Hippocampus

Control  Bilateral Atrophy
Quantification of regional atrophy in Korsakoff p’s

Colchester, Kopelman et al, 2001

C = controls
FF = focal frontal lesions
HE = herpes encephalitis
K = Korsakoff
Summary: MRI Volumetric Findings

1. **Korsakoff patients**
   - thalamic (and mammillary body) loss of volume
   - no significant medial temporal atrophy

2. **Herpes encephalitis patients**
   - severe medial temporal atrophy
   - no significant thalamic atrophy

*Colchester et al., JNNP, 2001*
FDG-PET in 12 KORSAKOFF PATIENTS
(Reed, Kopelman et al, 2003):
What are the neuroimaging correlates of Anterograde and Retrograde Amnesia?
Anterograde Memory / MRI Correlations
(40 amnesic patients, including 13 with the Korsakoff syndrome):

Correlation between ‘memory factor’ (derived from a factor analysis)
and total hippocampal volume: $r = 0.70$, $P < 0.002$.

<table>
<thead>
<tr>
<th>Table 2 Anterograde memory tasks: correlations with MR measures</th>
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<tr>
<td><strong>GMQ</strong></td>
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<td>Whole brain</td>
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<td><strong>Word recall</strong></td>
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<td><strong>Word recognition</strong></td>
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<td><strong>Picture recognition</strong></td>
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<td><strong>Brown-Peterson</strong></td>
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<td>Verbal</td>
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<td>Visual (Corsi blocks)</td>
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<td><strong>Total hippocampal</strong></td>
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* $p<0.05$; ** $p<0.01$, two tailed t test.
Predictors of *Retrograde Amnesia* in Korsakoff and Alzheimer patients.

1. **ANTEROGRADE MEMORY**
   (R.M.Q. x A.M.Q.): 21%

2. ‘FRONTAL’ / EXECUTIVE TESTS
   (Cog. Estims, FAS, Birds & Colours): 64%

Korsakoffs: 68.5%

Alzheimers: 57%

*Kopelman* *Brain* (1991)
**Retrograde Amnesia** x MRI regional brain volumes in 40 memory-disordered patients.

**Multiple Regression:**

**Frontal** + Thalamic + Medial Temporal MRI volumes predicted:

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<th>Diencephalic group:</th>
<th>Frontal group:</th>
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<tbody>
<tr>
<td>Autobiographical incident variance</td>
<td>60.1%</td>
<td>59.7%</td>
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<tr>
<td>Personal semantic fact variance</td>
<td>59.2%</td>
<td>68.0%</td>
</tr>
<tr>
<td>News event recall variance</td>
<td>47.9%</td>
<td>37.9%</td>
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*Kopelman et al Hippocampus, 2003*
Hypothesis:

• Mammillo-thalamic pathology $\rightarrow$ ‘consolidation’ deficit in new learning, and thereby anterograde amnesia?

• Frontal atrophy $\rightarrow$ superimposed retrieval deficit and retrograde amnesia?
What is Confabulation?
CONFABULATION

• **False or erroneous memories** arising in the context of organic amnesia. The memories may be false in themselves or ‘real’ memories jumbled and confused in temporal context and retrieved inappropriately.

• **Spontaneous** = a persistent, unprovoked outpouring of erroneous memories

• **Momentary / provoked** = fleeting intrusion errors or distortions in response to a challenge to memory, such as a memory test.

*Kopelman (1987) after Berlyne (1972)*
**MOMENTARY / PROVOKED CONFABULATION**

*Defined* in terms of fleeting intrusions or distortions adding irrelevant or inaccurate material.

**Kopelman (1987):**
Administration of Logical Memory test (Anna Thompson story) to Korsakoffs, Alzheimers, controls.

<table>
<thead>
<tr>
<th>Mean Scores</th>
<th>Immediate</th>
<th>45mins</th>
<th>1 week</th>
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<tbody>
<tr>
<td>Controls</td>
<td>10.2</td>
<td>8.7</td>
<td>6.3</td>
</tr>
<tr>
<td>Korsakoff p’s</td>
<td>4.1</td>
<td>0.4</td>
<td>not done</td>
</tr>
<tr>
<td>Alzheimer p’s</td>
<td>3.2</td>
<td>0.3</td>
<td>not done</td>
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Momentary Confabulation: Intrusion Errors / Distortions

Intrusion errors / distortions
- Korsakoff p’s: 50% of subjects
- Alzheimer p’s: 44% of subjects
- Healthy S’s: 50% of subjects

Examples:
- “Jack Brown took his wife down to Brighton” – K, 45 min recall.
- “She stole or found a purse, the object in mind being to feed her children” – A, immediate recall.
- “[She] stole £15 and was stopped by the police” – C, 1 week recall.

I.e. a normal response to a ‘weak’ or failing memory?
Spontaneous Confabulation:

• “RJ’s confabulation is not limited to test situations. He confabulates in interacting with therapists, fellow patients, and his family. For example, one weekend while at home with his family he sat up in bed and turned to his wife, asking her, ‘Why do you keep telling people we are married?’ His wife explained that they were married and had children, to which he replied that children did not necessarily imply marriage. She then took out the wedding photographs and showed them to him. At this point he admitted that the person marrying her looked like him but denied that it was he.”

Baddeley and Wilson, 1986.
Spontaneous Confabulation

1. **Luria (1976)**
   - Medial frontal lesions → “irrelevant associations … contamination … irrelevant impressions and confabulation in sharp contrast to the slight disability of the patients [in anterograde memory] … [a] gross disturbance of their active recall”.

2. **Stuss et al (1978)**
   - 5 p’s with fantastic /spontaneous confabulation
   - EEG’s, CT, psych testing. All showed evidence of frontal pathology
   - All showed severe Card Sorting impairment
   - Improvement in WMS from 87 to 112 in one patient → no change in confab’n.

   - Confabulation improved as frontal/executive tests improved
     (Card Sorting, Cognitive Estimates).

   - Frontal lobe lesions → Confabulation or poor ‘fluency’ on memory retrieval.

   -- Reviews: Ventro-medial and/or Orbito-frontal lesions → confabulation.
Fig. 3 Lesion overlap for the ACoA controls (n = 7; left) and confabulating patients (n = 4; right) superimposed on a template MRI scan. Colour bars represent the number of patients with lesions that overlap a particular region, with purple being one patient and red being all patients (four in the confabulation group and seven in the ACoA control group). Image was created using MRicro
Confabulating patient with voltage-gated potassium channel encephalopathy (Morvan’s syndrome): FDG PET.

Reduced FDG uptake compared with 20 normal volunteers: uncorrected p<0.001

Toosy ... Kopelman, Andrews, JNNP, 2008
Total confabulations on the Dalla Barba Confabulation Battery by location of lesion in 38 patients with frontal lesions, 16 with posterior lesions & 50 controls.
Theories of Confabulation

1. **Context Memory Confusions** (esp. temporal)  
   / Source or ‘reality’ monitoring deficits *e.g.* Schnider;

2. **Trace Specification / Verification theories**  
   *e.g.*, Deficits in strategic retrieval & pre-conscious  
   post-retrieval monitoring, *e.g.* Gilboa & Moscovitch;

3. **Motivational theories**, *e.g.* Fotopoulou & others;

4. **Interactionist theories** (combination of factors), *e.g.* Kopelman.
1: Temporal Context Memory Confusions

**Korsakoff (1889):**

Confusion of “old recollections with present impressions.”

**Eg:**

“In telling of something about the past, the patient would suddenly confuse events and would introduce the events related to one period into the story about another period…

Telling of a trip she had made to Finland before her illness and describing her voyage in fair detail, the patient mixed into the story her recollections of Crimea, and so it turned out that in Finland people always eat lamb and the inhabitants are Tartars.”

*Compare: Moll, 1915; Van der Horst, 1932; Talland, 1965; Victor, Adams & Collins, 1971*
Temporal Context / Source Monitoring Deficits:

- Differentiation of ‘spontaneous confabulators’ from amnesic patients on a temporal context memory task, but not on memory/executive tasks.
- Subsequently interpreted in terms of reality monitoring and a dysfunctional ‘filter’ in orbito-frontal cortex.

**Dalla Barba et al (1997)**
- ‘temporal consciousness’ intact, but malfunctioning
- patients aware of past, present, future (contrast severe amnesia)
- but employ only the most stable elements in long-term memory
- Very often these consist of early memories.
SCHNIDER et al., (Brain) 1996:

2 ‘runs’ of a Continuous Recognition task.

In the 2nd ‘run’, previous distractors became targets, & targets distractors.

This provokes false positive responses in saying which items had been seen before within that ‘run’.

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(Compare Gilboa et al., 2006)

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Fig. 2 Performance in the three continuous recognition tests (Experiment 2). Recognition scores are calculated as: hits – false positive alarms.

Fig. 3 Temporal order recognition failure (Experiment 3) measured as the increase of the relative number of false positives in the second run of the meaningful designs recognition test, in Experiment 2, i.e. \((FP_{2}/hits_{2}) - (FP_{1}/hits_{1})\) with \(FP_{1,2} = \) false positive alarms in run 1,2 and \(hits_{1,2} = \) true positive alarms (hits run1,2).
2: Trace Specification / Verification deficits.

Burgess & Shallice (1996):
- **Descriptor** → Trace specification $\neq$ inappropriate retrieval
- **Mediator** → Strategic control $\neq$ implausible/fantastic responses
- **Editor** → checking vs. task requirements $\neq$ errors

Schacter, Norman, Koutstaal (1998):
- Impaired ‘binding’ of features $\leftrightarrow$ momentary
  ± impaired pattern separation $\leftrightarrow$
- **Impaired retrieval** $\leftrightarrow$ Confabulation
  – focussed description $\leftrightarrow$
  – post-retrieval monitoring $\leftrightarrow$ spontaneous

Moscovitch & Melo (1997):
- Faulty cue-retrieval $\rightarrow$ retrieval errors
- Impaired strategic search $\rightarrow$ misleading cues $\rightarrow$ inappropriate memories
- Defective monitoring $\rightarrow$ errors not edited out

Gilboa, Moscovitch et al. (2006):
- Impaired strategic retrieval and pre-conscious post-retrieval monitoring.
“The explanations derived from the confabulations make more bearable the largely indifferent attitude of her relatives. This, coupled with her glowing views of lengthy time periods from her remote past, transforms the present into a time of harmony and comfort rather than discord and distress. She is aware that people do not now engage her in conversation…OP’s confabulations rewrite her personal history so that both the remote and recent past provide support for her in a difficult period…

Her often repeated statement when referring to some past period, that she had ‘wonderful friends’ attests to this…Negative events…can be recast, in a better light, by the beliefs emanating from her confabulated memories.”

*Cf Blanche in ‘Streetcar Named Desire’*
4: Interaction (multifactorial) theories

**Johnson et al (1997):**
- failed to differentiate confabulator from 3 frontal patients on source monitoring tasks

**Confabulation =**
- vivid imagination
- inability to retrieve autobiographical memories systematically
- source monitoring impairment

**Kopelman, Ng & Van den Brouke (1997):**
Confabulation across episodic, personal semantic, and semantic memory
- temporal context memory errors, esp in episodic memory;
- perseverations, esp. in semantic memory;
- instantaneous, unchecked responses to immediate social and environmental cues.
SUMMARY: CONFABULATION

1. Spontaneous:
   – Can be profuse, bizarre, preoccupying, and held with absolute conviction.
   – Associated with (ventro-medial and orbito-) frontal pathology.
   – May reflect:
     • confusions in temporal context
     • faulty trace specification / verification (monitoring)
     • perseverations esp. in semantic memory
     • underlying motivational and emotional biases.

2. Momentary / provoked:
   – Fleeting distortions / intrusion errors
   – Seen in healthy subjects when memory ‘weak’.
Conclusions
Conclusions: the alcoholic Korsakoff syndrome.

- Neuronal loss, gliosis, micro-haemorrhages in paraventricular & peri-aqueductal regions plus cortical atrophy.

- Lesions in anterior thalamus, mammillary bodies, mammillo-thalamic tract critical to anterograde amnesia.

- MRI shows atrophy in these circuits; atrophy in the hippocampus more controversial. PET shows focal regional hypometabolism.

- Main neuropsychological deficit in anterograde amnesia is in ‘acquisition’ or ‘consolidation’

- Accelerated forgetting can be shown between approx 20 secs and 10 mins on recall memory tests.

- Retrograde amnesia extends back 20-25 years, shows a steep temporal gradient, and may reflect a ‘superimposed’ frontal retrieval deficit.
Conclusions:

• **Korsakoff syndrome and confabulation** not necessarily linked:

• **Momentary confabulation** is seen in many amnesic patients (and healthy subjects), not just Korsakoff patients.

• **Spontaneous confabulation** is often seen just in the confusional (Wernicke) phase of the disorder, not in the chronic Korsakoff phase.

• **Spontaneous confabulation** is related to orbito-frontal and ventro-medial pathology.

• When seen in the chronic phase of the **Korsakoff syndrome**, there is usually fairly extensive concomitant frontal pathology.