Alcohol-related cognitive disorders: Korsakoff’s syndrome or alcohol-related dementia?

Roy P.C. Kessels, PhD
Professor of neuropsychology & clinical neuropsychologist

Content – alcohol, cognition and the brain

- Korsakoff’s syndrome
  - Definition KS and WE
  - Epidemiology
  - Cognitive profile
  - Brain abnormalities
- Alcohol-related dementia
  - Proposed criteria
  - Evidence pro and con
- Ethanol neurotoxicity
  - The continuity hypothesis
- Alcohol as protective factor for cognitive decline?
- Screening for cognitive impairment in AUD
Korsakoff’s syndrome

- No generally accepted definition (Sergei Korsakoff, 1887-1891)
- Victor et al. (1989): “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”
- Addition by Kopelman et al. (2009): “resulting from nutritional depletion, ie, thiamine deficiency”

- Severe and irreversible amnesia
- With a sudden onset (Wernicke encephalopathy)
- Mostly seen in chronic alcoholics

Wernicke encephalopathy

- Clinical diagnosis made using criteria by Caine et al.
- Can be treated by large quantities of thiamine, may fully recover
- Seen in chronic alcoholics, but also hyperemesis gravidarum, starvation, and all kinds of gastrointestinal diseases, AIDS and after bariatric surgery
- WE as diagnosis is often missed
- Treatment delay or lack of treatment: KS may be the residual syndrome

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>As evidenced by one or more of the following</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary deficiencies</td>
<td>- Undernutrition (body mass index &lt; 2 SD below normal)</td>
</tr>
<tr>
<td></td>
<td>- A history of grossly impaired dietary intake</td>
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<tr>
<td></td>
<td>- An abnormal thiamine status</td>
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<tr>
<td>Oculomotor abnormalities</td>
<td>- Ophthalmoplegia</td>
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<td></td>
<td>- Nystagmus</td>
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<td></td>
<td>- Gaze palsy</td>
</tr>
<tr>
<td>Cerebellar dysfunction</td>
<td>- Unsteadiness or ataxia</td>
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<td></td>
<td>- Abnormalities of past pointing</td>
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<td></td>
<td>- Dysmetakinesia</td>
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<td></td>
<td>- Impaired heel-shin testing</td>
</tr>
<tr>
<td>Either an altered mental state or Mild memory impairment</td>
<td>- Disorientation in two or three fields</td>
</tr>
<tr>
<td></td>
<td>- Confused</td>
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<td></td>
<td>- An abnormal digit span</td>
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<tr>
<td></td>
<td>- Comatose</td>
</tr>
<tr>
<td></td>
<td>- Failure to remember two or more words in the four-item memory test</td>
</tr>
<tr>
<td></td>
<td>- Impairment on more elaborate neuropsychological tests of memory function</td>
</tr>
</tbody>
</table>

Notes: When two or more of these four criteria apply, the clinical diagnosis of WE is made.
Brain imaging during the Wernicke encephalopathy stage

© Sullivan & Pfefferbaum, 2008

Epidemiology of Korsakoff’s syndrome

- Little research, no recent data
- Prevalence 3-5 cases per 10,000 inhabitants (NL)
- Annual incidence 0.5-0.65 per 10,000 inhabitants (Scotland)
- Age of onset ~40-60 (but younger and older onset has been reported)
- Incidence lower because of thiamine supplementation?
Korsakoff’s syndrome: more than just a “diencephalic amnesia”

**Characteristics:**
- Amnesic syndrome
- Executive dysfunction
- Personality changes and other neuropsychiatric symptoms
- Confabulations
- Lack of insight

**VIDEO patient**
© 1991 RVU/NTR Documentary “Gehoorzame Centimeter”
Anterograde amnesia

- Inability to store and retrieve new information
- Affecting episodic memory (everyday memory, “what, where and when”)
- Contextual confusion (target information related to wrong time and place)
- Increased (proactive) interference
- Can be demonstrated with any neuropsychological memory test
  - Delayed recall
  - Recall vs recognition
  - Both verbal and nonverbal
  - Ecological validity

Retrograde amnesia with temporal gradient

Rensen et al. 2017

Albert et al. 1974
Executive dysfunction

Confabulation behaviour

- **Provoked**: incorrect response to a question or situation in which a person feels compelled to say something ("where are we now?" – "we’re in a hotel")

- **Spontaneous**: occur without a trigger, patient acts accordingly (e.g., suitcased packed to go to a meeting with the boss of Shell)

- Not just “filling in memory gaps” due to amnesia, but result of temporal confusion, retrieval deficit, and impaired reality monitoring

- Spontaneous confabulations diminish over time, provoked confabulations still present in chronic phase

(Kopelman, 1987)
Nijmegen-Venray Confabulation List (NVCL-20)

Rensen et al., *Clinical Neuropsychologist* 2015
www.roykessels.nl/nvcl-20

<table>
<thead>
<tr>
<th>Confabulation measures</th>
<th>KS</th>
<th>ALC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVCL-20 (n = 28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>35.73 (13.9)</td>
<td>24.15 (6.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Spontaneous confabulation</td>
<td>14.0 (6.4)</td>
<td>10.3 (2.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Provoked confabulation</td>
<td>7.5 (2.8)</td>
<td>4.5 (2.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Memory and orientation</td>
<td>9.3 (4.6)</td>
<td>5.7 (1.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Lack of illness insight

Table S1 English version of the Q8

<table>
<thead>
<tr>
<th>Q8 questions</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Why are you here?</td>
<td></td>
</tr>
<tr>
<td>2. Do you feel that you are ill?</td>
<td></td>
</tr>
<tr>
<td>YES/NO</td>
<td></td>
</tr>
<tr>
<td>3. Which disease or disorder do you have?</td>
<td></td>
</tr>
<tr>
<td>YES/NO</td>
<td></td>
</tr>
<tr>
<td>4. What is the cause of this?</td>
<td></td>
</tr>
<tr>
<td>YES/NO</td>
<td></td>
</tr>
<tr>
<td>5. Do you suffer psychologically or do you experience feelings of guilt?</td>
<td></td>
</tr>
<tr>
<td>YES/NO</td>
<td></td>
</tr>
<tr>
<td>6. Do you experience limitations in your professional life, your family life, or in your social life?</td>
<td></td>
</tr>
<tr>
<td>YES/NO</td>
<td></td>
</tr>
<tr>
<td>7. How can we help you?</td>
<td></td>
</tr>
<tr>
<td>YES/NO</td>
<td></td>
</tr>
<tr>
<td>8. Do you think you can be treated?</td>
<td></td>
</tr>
<tr>
<td>YES/NO</td>
<td></td>
</tr>
<tr>
<td>Q8 total score</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Adapted and translated from Bourgeois ML, Kuklick H, Jia E. Validation de l’échelle d’insight Q8 en évolution de la conscience de la maladie chez 121 patients hospitalisés en psychiatrie [Validation of the insight Q8 scale and evolution of the awareness disorder in 121 psychiatric patients]. *Ann Med Psychol* 2002;160(12):517-522.

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Walvoort et al., *Neuropsychiatric Disease and Treatment* 2016;12:1609-1615
Neuropsychiatric symptoms

NPI-Q: Neuropsychiatric Inventory – Questionnaire for informants

Intact cognitive functions in KS

Emotional memory

- 9/11 study in KS 7 months after the event (Candel et al., 2003)
- >67% of the patients remembered the event ('emotional tagging' intact)
- Including vivid recollection of contextual details ("flashbulb memories")
- But less details than healthy controls, and less consistent
Intact cognitive functions in KS

Implicit learning / procedural memory

- Serial reaction time task (motor learning) (Van Tilborg…Kessels 2011)
- Implicit memory for object locations (Postma…Kessels 2008)
- Everyday skills through ‘errorless learning’ (Oudman et al., 2015; Rensen…Kessels 2017)

Intact cognitive functions in KS

“Despite the severity of Korsakoff patients' memory impairments, their intellectual functions, as measured by standardized IQ tests, often remain relatively intact” (Butters & Cermak, 1980, p. 7)

- Intelligence not a unitary construct: fluid vs crystalized intelligence
- Fluid intelligence and executive function overlapping domains (Van Aken et al., 2016)
<table>
<thead>
<tr>
<th></th>
<th>KS</th>
<th>ALC</th>
<th>non-ALC</th>
<th>$p_{KS\text{-non-ALC}}$</th>
<th>$p_{KS\text{-ALC}}$</th>
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<tbody>
<tr>
<td><strong>WAIS-IV</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>FSIQ</td>
<td>75.1 (12.2)</td>
<td>76.8 (12.3)</td>
<td>84.4 (16.6)</td>
<td>.587</td>
<td>.012*</td>
</tr>
<tr>
<td><strong>Index scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCI</td>
<td>84.2 (15.3)</td>
<td>86.3 (14.8)</td>
<td>88.4 (18.4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PRI</td>
<td>75.4 (10.0)</td>
<td>78.0 (11.6)</td>
<td>87.7 (18.2)</td>
<td>.011*</td>
<td>1.00</td>
</tr>
<tr>
<td>WMI</td>
<td>84.5 (15.4)</td>
<td>79.8 (15.8)</td>
<td>84.4 (16.6)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>PSI</td>
<td>70.1 (18.0)</td>
<td>75.5 (17.2)</td>
<td>84.4 (13.4)</td>
<td>.001*</td>
<td>.514</td>
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<tr>
<td><strong>Subtests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information</td>
<td>7.3 (2.9)</td>
<td>7.4 (3.0)</td>
<td>7.8 (3.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Block Design</td>
<td>5.5 (2.0)</td>
<td>6.1 (2.2)</td>
<td>7.7 (3.3)</td>
<td>.003*</td>
<td>.422</td>
</tr>
<tr>
<td>Matrix</td>
<td>6.2 (2.7)</td>
<td>6.6 (2.5)</td>
<td>8.2 (3.7)</td>
<td>.011*</td>
<td>.539</td>
</tr>
<tr>
<td>Reasoning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Puzzles</td>
<td>6.0 (2.1)</td>
<td>6.5 (2.7)</td>
<td>8.1 (3.3)</td>
<td>.007*</td>
<td>.574</td>
</tr>
<tr>
<td>Digit Span</td>
<td>7.5 (3.5)</td>
<td>6.0 (3.2)</td>
<td>7.4 (3.3)</td>
<td>1.00</td>
<td>.161</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>7.2 (2.5)</td>
<td>7.1 (2.7)</td>
<td>7.2 (3.1)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Symbol Search</td>
<td>4.7 (3.0)</td>
<td>5.6 (3.4)</td>
<td>7.3 (2.6)</td>
<td>.001*</td>
<td>.193</td>
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<tr>
<td>Coding</td>
<td>4.9 (3.2)</td>
<td>5.9 (2.8)</td>
<td>7.2 (2.6)</td>
<td>.001*</td>
<td>.255</td>
</tr>
<tr>
<td><strong>NART-IQ</strong></td>
<td>90.9 (17.1)</td>
<td>86.3 (16.7)</td>
<td>88.2 (13.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intact cognitive functions in KS

“Despite the severity of Korsakoff patients’ memory impairments, their intellectual functions, as measured by standardized IQ tests, often remain relatively intact”(Butters & Cermak, 1980, p. 7)

– Intelligence not a unitary construct: fluid vs crystalized intelligence
– Fluid intelligence and executive function overlapping domains (Van Aken et al., 2016)
– KS patients show impaired processing speed and fluid abilities (Haalboom et al., submitted), but crystallized intelligence is preserved
Brain abnormalities in KS
Histopathological evidence from New South Wales Tissue Resource Centre

<table>
<thead>
<tr>
<th>Measurement</th>
<th>N</th>
<th>AE</th>
<th>AE - WE</th>
<th>AE - WE</th>
<th>KS</th>
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<tbody>
<tr>
<td>Cortical neurons</td>
<td>100</td>
<td>77</td>
<td>84</td>
<td>84</td>
<td></td>
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<tr>
<td>(superior frontal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical neurons</td>
<td>100</td>
<td>81</td>
<td>75</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>(dendritic Arbor)</td>
<td></td>
<td></td>
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<tr>
<td>Hippocampal neurons</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
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<tr>
<td>(mediodorsal)</td>
<td></td>
<td></td>
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<tr>
<td>Thalamus</td>
<td>100</td>
<td>100</td>
<td>92</td>
<td>92</td>
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<tr>
<td>(anterio)</td>
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<td></td>
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</tr>
<tr>
<td>Mamillary bodies</td>
<td>100</td>
<td>100</td>
<td>93</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Basal forebrain</td>
<td>100</td>
<td>100</td>
<td>92</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Locus ceruleus</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Medial raphe</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Dorsal raphe</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

AE = alcoholic encephalopathy
WE = Wernicke encephalopathy
KS = Korsakoff’s syndrome


Grey and white matter changes in alcoholic with and without KS

AL = chronic alcoholics without Korsakoff’s
KS = chronic alcoholics with Korsakoff’s
CS = control subjects

**Grey matter:**
(A) AL < control subjects (CS);
(B) KS < CS;
(C) AL < CS and KS < CS.

**White matter:**
(D) AL < CS;
(E) KS < CS;
(F) AL < CS & KS < CS.

Note: AL mean 12.7 days of abstinence

DSM-5 and alcohol-related cognitive disorders

Korsakoff’s syndrome in the DSM-5:
• Alcohol-induced Major Neurocognitive Disorder
• Amnestic-confabulatory type

Criteria for Major Neurocognitive Disorder (~dementia):
• Deficits in one or more cognitive domains
• Decline from previous level of functioning
• Interference with independence in daily living

Alcohol-related dementia (ARD)
• Criteria proposed for ARD by Oslin et al. (1998)

• “Probable ARD”

Required:
• Clinical diagnosis of dementia >60 days abstinence
• >5 years >35 †/28 † standard drinks/week (<3 years prior to onset dementia)

Supportive:
• Alcohol-related somatic complications (hepatitis, renal disease …)
• Ataxia
• Cognitive impairment improves or stabilizes >60 days
• Ventricular/sulcal dilation on MRI improves >60 days
Controversy

• ARD is, however, a controversial concept

PRO

• Alcohol use more common in dementia patients than those without dementia
• Cognitive impairments frequently demonstrated in patients with alcohol-use disorder (AUD)
• Animal studies have demonstrated neuropathology due to alcohol

CON

• Oslin criteria include patients with Korsakoff’s syndrome
• Criteria have not been widely accepted
• Mainly because of the lack of distinct pathophysiology
• And many cases described in the literature have been recently detoxified

The effects of alcohol on the brain: “ethanol neurotoxicity”?

• WE can also occur in non-alcoholic patients
• Progression from WE to KS unrelated to alcohol consumption
• Both animal studies and clinical studies in humans show that the effects of ethanol neurotoxicity are reversible
• Well-nourished and otherwise healthy individuals with AUD show full cognitive recovery 1-2 after abstinence
• AUD also associated with lifestyle risk factors (cerebrovascular, traumatic brain injury, poly-drug use) and co-morbidity (hepatitis, renal dysfunction)
• Reduction in white matter most common finding in AUD \(\rightarrow\) demyelinisation, but remyelinisation occurs after abstinence
Alcohol-related cognitive disorders

- Executive functions
  - Response inhibition
  - Risk taking
  - Decision making
  - Abstract reasoning
  - Mental flexibility
- Memory
  - Learning & retrieval efficiency
  - No amnesic syndrome
- Visuospatial functions
  - Often with an executive component (e.g., Rey's figure)
- Social cognition
  - Affective prosody
  - Perception of facial expressions
  - Interpersonal interaction

Is (moderate) alcohol use protective for cognitive decline?

- U-shaped curve often reported

Altogether, most studies observed a U-shaped relation of alcohol consumption and cognitive function: heavy consumption of alcohol alters brain functions and decreases cognitive performance, moderate and light consumption may have protective impact. In many studies, total abstainers show an inferior cognitive performance than people with moderate or light consumption.

Gutwinski et al. *Pharmacopsychiatry*, in press
Whitehall II imaging study

- Alcohol use negatively correlated with hippocampal volume and white-matter integrity (DTI FA ↓, MD/RD/AD↑)
- And related to worse performance on lexical fluency

Topiwala et al. BMJ 2017;357:j2353

Moderate alcohol consumption and cognitive decline

Dose-dependent association with letter fluency

But not with:
- Montreal Cognitive Assessment
- Episodic memory → MTL
- Semantic fluency
- Naming
- Executive function

Plus:
Participants are not abstinent

Topiwala et al. BMJ 2017;357:j2353
Is there a dose-response relationship?

- Continuity hypothesis (Butters & Brandt)
  - Quantity of alcohol intake and duration predict the severity of the cognitive disorder
  - Continuity hypothesis also mentioned as cause of the memory disruptions with temporal gradient in Korsakoff’s: old memories are better preserved than recent ones, with a gradient

- However: no support for this continuity hypothesis
  - ‘Uncomplicated alcoholics’ have reversible cognitive deficits
  - Korsakoff’s syndrome caused by thiamine deficiency, not alcohol in itself
  - No evidence for dose-response relation between alcohol use and (irreversible) cognitive deficits or brain abnormalities

- Current view: a combination of factors explains the brain dysfunction

The effects of alcohol on the brain

- Estimate: 50% of people with alcohol-use disorder (AUD) have cognitive impairments
- 10% have severe cognitive impairments (incl. Korsakoff’s syndrome)

Mechanisms:

- Direct neurotoxic effect: gray and white matter volume reduction (but reversible)
- Indirect neurotoxic effect: high calcium concentrations may damage neurons after sudden withdrawal/abstinence
- Indirect effect of vitamin deficiency (B1/thiamine)
- Indirect effect of comorbidities (hepatitis, multiple drug use, traumatic brain injury, cerebrovascular risk factors)

In clinical practice, it can be difficult to assess the individual contributions of these factors
Screening for cognitive impairments in AUD

- Not feasible to perform neuropsychological assessment in all AUD patients
- A short screening for cognitive deficits would be helpful
- MMSE poor psychometric properties (e.g., Nieuwenhuis-Mark, 2010)
- Montreal Cognitive Assessment (MoCA) possible candidate
  - Widely used
  - MoCA available in many languages
  - Parallel version to prevent test-retest effects
  - Validity of cut-off score established
  - Several studies examined MoCA in addiction care

(www.mocatest.org)
MoCA in AUD

<table>
<thead>
<tr>
<th>Cognitive Domain (range)</th>
<th>AUD (N = 391)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive Functioning (0-2)</td>
<td>1.27 (0.68)</td>
</tr>
<tr>
<td>Visuospatial Abilities (0-4)</td>
<td>2.73 (0.95)</td>
</tr>
<tr>
<td>Attention Concentration Working Memory (0-6)</td>
<td>5.44 (0.95)</td>
</tr>
<tr>
<td>Language (0-6)</td>
<td>4.96 (0.98)</td>
</tr>
<tr>
<td>Abstract Reasoning (0-2)</td>
<td>1.51 (0.64)</td>
</tr>
<tr>
<td>Memory (0-5)</td>
<td>3.21 (1.56)</td>
</tr>
<tr>
<td>Orientation (0-6)</td>
<td>5.76 (0.62)</td>
</tr>
<tr>
<td>MoCA Total (0-30)</td>
<td>25.30 (3.23)</td>
</tr>
<tr>
<td>Below cut-off of 24 (%)</td>
<td>134 (34.3%)</td>
</tr>
</tbody>
</table>

• MoCA shows acceptable sensitivity and reliability compared to extensive neuropsychological assessment in (A)UD (Ridley et al., 2017; Bruijnen et al., in preparation; Ewert et al., in press)
• But adjustment for education level under debate
• Cannot replace an extensive neuropsychological assessment, but should be used as a first screen → FU with neuropsychological assessment recommended

The effects of alcohol on the adolescent brain

• TRAILS Study (TRacking Adolescents’ Individual Lives Survey); Trimbos & Utrecht University
• 2,230 Dutch adolescents aged 11 (in 2000)
• T2: aged 13; T3: aged 16; T4: aged 19
• Group subdivided into 6 groups of drinkers (abstainers up to very heavy drinkers: >15 units/week for 4 years)
• Cognitive functions tested on T4
• No differences between groups
• However: no MRI measurements, duration of follow-up very limited
• No reason to revise alcohol use policy → more research needed
To conclude…

• Korsakoff syndrome result of thiamine deficiency
• Not only amnesia, but also other domains affected

• ARD ill-defined diagnostic label
• Effects of alcohol on cognition and the brain reversible after prolonged abstinence
• Alcohol as one of the risk factors for later dementia (lifestyle)

• Cognitive deficits in AUD relevant to detect
• MoCA valid and reliable as a first screen → FU neuropsychological assessment

• Alcohol and the adolescent brain: more research needed
Acknowledgments

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Loes van Aken, PhD

King’s College London
Michael Kopelman, PhD
Ellen Migo, PhD
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