Wada Test
Intracarotid Amobarbital Procedure (IAP)

Elisabeth Pauli
Epilepsy Center,
Director Prof. H. Stefan
Dept of Neurology
University Hospital Erlangen
Wada Test
Intracarotid Amobarbital Procedure (IAP)

Content:
1. history, basic principles
2. current role
3. methodology, effects, risk
   1. protocols
   2. evaluation
3. non-invasive alternatives
   (MEG, fTCD, RTMS, SPECT, PET)
4. fMRI for language and memory
Wada Test

History

- **1949 Juhn Wada** introduced his method for the lateralization of language

- **1962 Brenda Milner** adapted the protocol for the assessment of memory and published „study of short term memory after intracarotid injection of sodium amytal“

Since then the Wada test became a standard procedure in the neuropsychological evaluation for surgical treatment of TLE

*) W. van Emde Boas. Juhn A. Wada and the Sodium Amytal Test
**) http://www.psych.ualberta.ca/GCPWS/copyrightBar
Wada Test

**basic principle**

- Intracarotid application of sodium amytal in one of the cerebral hemispheres through transfemoral catheterization

- Functional inactivation of the ipsilateral hemisphere for up to 10 minutes

- The functions of the awake hemisphere are tested: mainly speech and language
The Wada Test (IAP) is used in the preoperative evaluation before epilepsy surgery:

- language lateralization
- to assess the risk of an amnesic syndrome postoperatively
- to assess the risk of material specific – memory deficits particularly verbal memory deficits

„gold standard“ for alternative methods e.g. fMRI
The relation between preoperative IAP scores and postoperative memory function could be repeatedly established:

Conclusion:

IAP provides a valuable predictor for memory decline in adults and children, particularly with respect to verbal memory decline after a left mesial temporal resection

(Loring et al., 1990; Kneebone et al., 1995; Jokeit et al., 1997; Bell et al., 2000; Chiaravalloti and Glosser, 2001; Stroup et al., 2003; Kirsch et al., 2005; Lee et al., 2005).
The Wada Test is also used in the preoperative evaluation for:

- **lateralization of the seizure focus**
  
  (Lancman et al., 1998; Lee et al., 2002; Cohen-Gadol et al. 2004)

- **lateralization of hemispheric dysfunction**
  
  “The IAT is useful in predicting lateralized focus but also bihemispheric onset as well”
  
  (Swearer et al. 1999)

- **prediction of postoperative seizure control**
  
  Prediction of postoperative seizure freedom: „memory asymmetry in the unexpected direction may signal poor surgical outcome after nondominant temporal lobectomy“
  
  (Kirsch et al. 2005)
Recent studies reported:

IAP not essential to predict memory decline after surgery especially in RTL cases, when the results of other noninvasive diagnostic tests are taken into account.

(Baxendale et al., 2006, Lineweaver et al., 2006)
The role of the IAP has been challenged by new, noninvasive technologies, in the first instance by structural and functional MRI.

Assumption: the integrity of the contralateral structures can be ensured by MRI and fMRI providing valuable data regarding amnesic risk. (Lencz et al., 1992; Baxendale et al., 1998; Kapur and Prevett, 2003; Woermann et al., 2003; Richardson et al., 2004; Janszky et al., 2005; Koepp and Woermann, 2005).

Yet currently clinical and research emphases shifted toward the importance of the IAP in the prediction of postoperative memory change (Stroup et al., 2003; Kirsch et al., 2005)
Resume
Despite controversies and uncertainties the Wada Test remains today his clinical value for the preoperative evaluation of memory and it plays the decisive role as gold standard for the evaluation of alternative techniques.
Wada Test: common practice

- 75 - 200 mg of Sodium Amobarbital injected by trans-femoral artery catheterization into one internal carotid artery. Selective injection in the anterior choroids artery or the posterior cerebral artery possible.

- **Angiography:** recognition of unexpected effects. Injection of 2-3 ml contrast agent at the same rate as the injection of the amytal to designate the affected area.

- **Simultaneous EEG monitoring:** documentation of functional changes in the ipsi- and contralateral hemisphere.

- **Video recording:** possibility to reanalyze the test afterwards.

- **Chronology:** both hemispheres are tested either in one session with a sufficient interval or on two successive days.
Wada Test: effects

- brief temporary contralateral hemiparesis
- hemianopsia contralateral
- EEG slowing
- if the speech dominant hemisphere is injected: aphasia for 2-3 minutes, followed by a recovery interval with dysphasia and paraphasia
- retained consciousness and ability to act with the contralateral arm
Risk of an arteriogramm:

Morbidity risk:  3 – 5%
- Risk of carotid artery dissection (0.7%, Lodenkemper et al. 2002)
- Cerebral infarction
- Arterial spasm with potential transient deficits
- Transient femoral neuropathy

Risks are greater for older people
Intention to perform angiography:

- Perfusion pattern may vary between patients: possible differences and anomalies in the vascular anatomy.
- Pathological connections between carotid- und vertebra-basilar supply area may result in narcosis of respiratory and cardiovascular centers in the brainstem.
- Speedy injections und enlarged contrast volumes may bear the risk for cross flow, which results in a not interpretable situation - Therefore the amytal injection has to be carefully adjusted.
Test condition: the areas crucial for memory are reliably anesthetized

- no reliably perfusion of the posterior 2/3 of the hippocampus and the parahippocampus.

But: depth electrodes and SPECT showed slowing and functional changes in the posterior hippocampus


memory items should be presented earliest in the test

(Jones-Gotman, 1987)
Wada Test
methodological considerations (3)

Both tests on the same day or on separate days?

- Reduced alertness with left sided (dominant) injection → influence on Wada memory scores (Meador et al. 1997).
- Bilateral tests with an interval of 30 - 60 minutes: lower memory scores for the second injection
- Separate days: comparable memory scores (Grote et al. 1999)

Adverse effect on alertness are more pronounced, if the dominant hemisphere is injected after the nondominant on the same day (Glosser et al. 1999)
Wada Test
methodological considerations (4)

Alternatively used anesthetics

- **Propofol** (Takayama et al 2004) adverse effects (30%)
- **Methohexital** (Buchtel et al. 2002)
- **Etomidate** (Jones-Gotman et al. 2005) very short acting

Half lives shorter << amytal !
Wada Test
methodological considerations (5)

**Caution** in patients taking *topiramate* or *zonisamide* (carbonic anhydrase inhibitors) - Failure of anesthetization (Bookheimer et al. 2005)

Failure to underestimate memory functions
Test protocols vary considerably between centers

**Presentation of items**
- before injection
- during narcosis

**Retrival**
- during narcosis
- after recovery
Wada Test
protocals in use


- Directly after injection (during narcosis): presentation of 8 items
  - 4 verbal
  - 4 visual
- during narcosis: test of recognition memory of 4 items
- after recovery: test of recognition memory for the residual 4 items

- Directly after injection assessment of language
- 2.5 min after injection: presentation of 5 memory items
- 15 minutes after injection: test of recognition memory (each item presented between 3 distractors)

Asymmetry scores and cut off values for passing or failing are used to predict postoperative memory loss
Erlanger protocol: Norm-value comparison
- Normal performance of a healthy left or right hemisphere?
- Indication of compensation?

Both hemispheres differentially specialized

Left hippocampus:
strong advantage for verbal memory –

Right hippocampus:
dominant for complex visual and spatial material
Wada Test
Erlanger Protocol

1. day:
training test without injection

2. + 3. day:
anaesthesia of the left or the right cerebral hemisphere

Dose:
Injection of 150 mg amobarbital via transfemoral catheter into the right or left internal carotid artery.

Angiography, simultaneous EEG monitoring and Video recording
Wada Test
Erlanger Protocol

Item presentation: at maximal sodium amytal effect, indicated by:

- EEG slowing
- contra-lateral hemiparesis
Wada Test

Erlanger Protocol  chronology of item presentation

1. counting starts directly before injection and carries on for the time of injection - followed by 2 simple commands

3. naming und memorizing of 5 pictures and 3 objects

4. presentation of 5 written words – reading/ hearing and memorizing

5. Token-Test form 2 and 3 (each with 5 Items)

6. repeating of 2 letters, 6 words und 2 sentences

7. reading of 5 sentences including detection of semantically and syntactically errors

8. counting backwards

Ca. 10 -15 min

Injection

after recovery: memory test
Wada Test
Erlanger Protocol

Type of memory items: double encodable

Memory assessment:
After recovery from anaesthesia: free recall and recognition.
Recognition performance is tested by forced choice using three distracters with each item.

Scoring:
Free recall:
each correct answer: 1 point
Recognition memory:
every correct choice 1 point

total memory score = free recall + recognition
Normal values:
obtained from the data base (N>200) for contralateral hemispheres in patients presenting with:

- unilateral mesial TLE
- IQ within the normal range (IQ >= 90)
- left sided speech dominant
- postoperative seizure free (Engel 1a)
Wada Test
**Erlanger Protocol, z-transformation**

left

right

normal values from healthy left hemispheres

normal values from healthy right hemispheres

z-transformation

(M = 0, SD = 1).

comparable scores
The functional integrity of the right TL is sufficient to prevent from global amnesia \( z (\text{memory right}) = 0 \)

In order to avoid verbal memory deficits we need indication that previously - early in life - reorganization had happened. Shift of verbal memory to the right mTL is even possible in left sided dominance. An indicator for reorganization would be a contralateral memory score higher than average \( z (\text{memory right}) \geq +1 \)
Wada Test

Erlanger Protocol  Testing contralateral compensational capacity

Contralateral compensation:
- no compensation: $z(\text{memory right}) < 0$
- compensation questionable: $z(\text{memory right}) \geq z(\text{memory left})$ but $z(\text{memory right}) < +1$
- contralateral compensation: $z(\text{memory right}) > z(\text{memory left})$ and memory (right) > 1
Verbal memory pre- and postoperative in relation to Wada Test prediction

Contralateral compensation predicted by Wada Test and verbal memory change

Analysis of variance for repeated measurements:
Interaction F=8.35, p=0.001
Wada Test

Videodemonstration
Wada Test

Noninvasive alternative methods for lateralization of language and memory
Wada Test

Alternatives for language lateralization
- transcranial magnetic stimulation (MTS, RMTS)
- MEG
- functional transcranial Doppler sonography or
- PET
- SPECT
- Functional MRI
Wada Test
Alternatives for language lateralization

- Repetitive transcranial magnetic stimulation (TMS / RTMS) for language lateralization and localization
  - Deactivation of cortical areas
  - RTMS able to lateralize language, but accuracy insufficient-
  overestimation of the frequency of bilateral or right hemisphere lateralization
  - adverse effects
**Wada Test**
Alternatives for language lateralization

- **MEG Magnet Encephalography**
  MEG: measurement of magnetic field changes associated with event-related brain activity.

  Excellent time resolution

  MEG is able to identify frontal and temporal language areas by appropriate activation paradigms

  Its concordance with the Wada test in identifying language dominance is demonstrated in several studies (Papanicolaou et al. (2004))
Independent clinical judgments based on MEG and Wada data showed a high degree of concordance (87%). Magnetoencephalography laterality judgments had an overall sensitivity of 98%, but a lower selectivity of 83%, which was due to the fact that MEG detected more activity in the nondominant hemisphere than was predicted based on the Wada test.

ANDREW C. PAPANICOLAOU, J Neurosurg 100:867–876, 2004
Typical activation profiles obtained in patients with left- (upper) or right-hemisphere dominance (lower), or bihemispheric representation of language function (center).

This region has been shown in previous studies to correspond with the receptive language–specific cortex in patients who, in addition to the Wada procedure, underwent electrocortical stimulation mapping within the dominant hemisphere.

A. C. PAPANICOLAOU, J Neurosurg 100:867–876, 2004
Wada Test
Alternatives for language lateralization

- Functional transcranial Doppler sonography (fTCD) for language lateralization

  Activation of language functions related to increased blood flow in the language dominant hemisphere

  fTCD: measurement of blood flow velocity in the middle cerebral arteries during language tasks.

  Good concordance with Wada Test (Knecht et al., 1998; Knake et al., 2003)

  Limitation of fTCD:
  15–21% subjects lack an acoustic temporal bone window for insonation of the middle cerebral artery.

  Too small samples.
Wada Test
Alternatives for language lateralization

- PET $^{15}$O-water positron emission tomography

PET identifies regional changes in cerebral blood flow. Used for functional mapping of higher cognitive processes. Used to lateralize and localize language functions.

Limitations:
- Availability, access to a cyclotron for ligand generation
- Radioactivity limits time for PET scans
SPECT:
Single Photon Emission Computed Tomography

Assessment of regional changes in cerebral blood flow by imaging the perfusion area of a intravenously injected radioligand. Usually: 99mTc-HMPAO (hexamethylpropylene amineoxime). By comparing activation and baseline regional blood flow, changes associated with activation can be localized and lateralized.

Up to now no comparisons with Wada tests.
fMRI in the presurgical neuropsychological evaluation

- fMRI for language lateralization and localization
- fMRI for memory lateralization
Neuronal activity leads to a large increase in blood flow, but the increase in oxygen consumption is much smaller.

- Increased level of oxygenated hemoglobin in the activated tissue.

Oxygenated and deoxygenated hemoglobin differ in magnetic properties, leading to local changes in the magnetic field homogeneity.

Local activation of neuronal cell populations show an increased signal relative to the inactivated (resting) state.

fMRI measures brain function in terms of changes in blood flow.
Non-invasive fMRI paradigms for language activation: word generation  semantic processing

Language lateralization by fMRI and IAT: impressive concordance rates - despite the use of different fMRI language tasks and IAT protocols (Baxendale 2002)

fMRI and Wada test: 90% concordant for identification of the language dominant hemisphere (Koepp and Woermann 2005)
Reproducibility of activated brain areas by verbal fluency in typical and atypical speech dominance

Schäfer I., Pauli E., Stefan H.
Dept. of Neurology, Center Epilepsy, University of Erlangen-Nürnberg, Schwabachanlage 6, D-91054 Erlangen, Germany

Results

The intraindividual activated brain areas were identical in both repetitions.

The number of activated pixels showed some variation between the two repetitions.
Frontal language areas can be successful activated during expressive language tasks.

Activation of temporal language areas are more challenging, requiring fMRI protocols including verb generation, comprehension and picture naming (Rutten et al. 2002).

Naming and reading are most at risk in dominant TL resection!

Reading paradigm group results overlaid on the normalized mean images in axial and coronal slices. Activation:
- fusiform gyrus bilateral
- middle temporal gyrus
- anterior temporal pole l>r

Deblaere et al. 2002
fMRI Language Localization

Although language lateralization by fMRI is a good option there are some open questions with respect to specificity and sensitivity:

- Are all areas activated by a particular fMRI paradigm really crucial necessary for language function? Meaning of variable amounts of right hemisphere activation.

- Are all areas involved in special language skills activated by a particular fMRI paradigm?
Assumption:
Failure to activate the left or right hippocampus reflects impaired functions

fMRI paradigms have been developed using dually encodable stimuli that normally show symmetrical activation of the hippocampal formation, against which asymmetric - dysfunctional - patterns could be compared

A task requiring retrieval of visuospatial information elicits interhemispheric differences in mesial temporal lobe activation which correctly lateralized the side of seizure onset in 90% of patients with unilateral TLE (Jokeit et al. 2001)

A visuospatial task reliably activates mesial TL structures: in controls bilateral activation, TLE patients 90% reduced activation on side of seizure focus (Detre et al. 2001)

Using a visuospatial task in unilateral TLE patients a larger activation was found on the contralateral side. The normal use of bilateral regions during memory retrieval is altered to asymmetry indicating disordered memory (Jantzky et al. 2004).
2. fMRI and verbal Memory

fMRI paradigms using verbal stimuli for memory:

During verbal encoding:
- left activation in healthy controls
- increased in the left hippocampal formation in right TLE
- reduced left hippocampal activation in LTLE
(Bellgowan, 1998)

During verbal retrieval
- bilateral activation right > left in LTLE and controls (more marked in controls)
- left prefrontal activations in all memory tasks in LTLE
- In a delayed retrieval condition bilateral poor activation in LTLE suggesting an inability to reactivate key memory areas.
(Dupont et al. 2000, 2001)
2. fMRI and verbal Memory

- In left hippocampal sclerosis preserved verbal memory were related to increased right hippocampal activation, indicating reorganization of function (Richardson et al. 2003).

- In left hippocampal sclerosis greater activity in the left hippocampus compared to the right predicted the extent of memory decline after left anterior temporal lobectomy (event-related verbal encoding fMRI study) (Richardson et al. 2004)
**Verbal memory in Wada Test and fMRI**

**Patient:** 48 y, male, seizures onset 8 y. EEG: left temporal

**Neuropsychology:** Language functions: normal, memory functions: normal verbal memory, low figural memory

**IAT:** language: left superior memory right, left hippocampal dysfunction

**fMRI:** encoding: right hippocampal activation

verbal memory shift to the contra-lateral right hippocampus despite leftsided speech dominance
Although the findings of studies to date are promising, fMRI memory tasks cannot be used alone to predict postoperative memory deficits based on the present data. There is a need for larger sample sizes with postoperative follow-up to determine the ability of fMRI to predict postoperative memory on an individual-patient basis

(Kimford & Meador, 2003)