Neurotoxicology

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- The nervous system is vulnerable to a wide range of insults from environmental or occupational toxins.

•Historical descriptions of neurotoxicity:

•lead poisoning
•homicidal use of arsenic
•glue-sniffer's neuropathy (hexacarbons)

MANIFESTATIONS OF NEUROTOXICITY

General principles

- There are multi pattern of neurotoxicity in nervous system(CNS or PNS or ...involvement)
- A dose-toxicity relationship exists in the majority of neurotoxic exposures.
- Typically : non focal, symmetric neurologic syndrome.
- There is strong temporal relationship between exposure and the onset of symptoms.
- In most cases recovery is possible.
- Multiple neurologic syndromes are possible from a single toxin
- Some toxins present with a pathognomonic neurologic syndrome.

Central Nervous System

- Acutely, the encephalopathy may be associated with alteration in the level of consciousness.
- Chronically, the primary symptoms may be cognitive and psychiatric.
- Some toxins cause relatively selective injury to the vestibular system or the cerebellum, resulting in dysequilibrium, vertigo, and gait or limb ataxia.
- Basal ganglia involvement may lead to an extrapyramidal syndrome of bradykinesia, tremors, and rigidity

Peripheral Nervous System

- Sensory disturbances
- Impairment of the deep tendon reflexes on physical examination
- Symmetric peripheral neuropathy (*polyneuropathy)*
- The hallmark of most polyneuropathies is the distal distribution of the clinical symptoms and signs.
- The most common syndrome is subacute onset of tingling or numbness experienced in a symmetric stocking-and-glove distribution.

Peripheral Nervous System

- Involvement of the motor nerve fibers(muscle atrophy and weakness).
- Appear first in the distal-most muscles (i.e., the intrinsic foot and hand muscles).
- More severe cases may involve muscles of the lower legs and forearms, leading to bilateral foot drop or wrist drop.

Neurotoxins

lead

- Paint
- Batteries
- Pipes
- Solder
- Cables,.....

Acute high level:

Headache ,tremor ,apathy ,lethargy

Lead

- Massive intoxication :

  Lead encephalopathy: lead blood levels of> 50-70 μg/dl

  -convulsions

  -Stupor

  -cerebral edema

  -coma

- Chronic low-level exposure : impaired intellectual development in children, decrease IQ ,behavior disturbance,….

Lead

- Classic description: bilateral wrist-drop and foot-drop.

(we can also see asymmetry here)

- The best known clinical syndrome is a predominantly motor neuropathy with little if any sensory symptoms.

- Toxicity also may manifest as a generalized proximal & distal weakness and loss of DTR.

- lead level > 40 μg/dl: ***Asymptomatic &*** NCV abnormalities.

Mercury

- Batteries
- Fungicides
- Electronics
- Contaminated fish
- Dental amalgam

Mercury

- Mercury poisoning causes a diffuse encephalopathy.
- Emotional lability, euphoria, anxiety, irritability….coma

- Organic, inorganic, metallic mercury :CNS disturbances (tremor, cerebellar ataxia, hearing Loss, visual field constriction, hyper reflexia and Babinski sign)

- Inorganic mercury: PNS (Neuropathy)
  - Acute = Guillain-Barre syndrome
  - Subacute = ALS

- Cerebellar ataxia is common, and patients may develop a fine postural tremor that begins in the extremities and then involves the face and tongue

Arsenic

- As wood preservatives
- Gallium arsenide in the semiconductor industry
- Defoliant and desiccant in agriculture

Arsenic

- The most common manifestation of neurotoxicity(acute or chronic)

  Peripheral neuropathy

- Massive dose:

  -acute: acute polyneuropathy (**1-3** weeks) = Guillain-Barre syn.

  -chronic: Symmetrical sensorimotor polyneuropathy (distal weakness>>proximal weakness)

  -Sensory and motor deficits spread proximally. Shoulder and pelvic girdle weakness, as well as gait ataxia

Arsenic

- Chronic low-level exposure (environmental or occupational sources) has been associated with more subtle impairment of **memory and concentration**.
- In exposed children, there are also reports of lower verbal performance and hearing impairment.

- Arsenic is detectable in blood and urine during ongoing exposure and may persist in urine for several weeks after a single massive exposure.
- With a low-level exposure, blood arsenic level returns to normal in about 12 hours, and urine arsenic clears within 48-72 hours after exposure.
- Arsenic remains detectable in hair and nails for months after exposure.

Carbon disulfide (CS2)

- Solvent in perfume production and varnishes
- In soil fumigants and insecticides
- Used in the production of viscose rayon, cellophane,, as a solubilizer for waxes and oils

Carbon disulfide (CS2)

- Acute :

  Dizziness, headache, delerium, mania…..convulsion, coma
- Chronic:

  Peripheral neuropathy presents with paresthesias and pain in the distal legs, loss of Achilles reflexes, Headache, fatigue, sleep dis.

Manganese

- Poisoning occurs most commonly in the mining, smelting, milling, and battery-manufacturing industries

Manganese

- The classic syndrome:
  extrapyramidal disorder (idiopathic Parkinson disease)
  tremor, rigidity, masked faces, and bradykinesias

- Neurologic deficits often continue to progress for many years after cessation of exposure

- Manganese-induced parkinsonism is usually
  - symmetrical
  - atypical features such as facial grimacing, early foot dystonia and gait disturbance(so called "cock-walk")
  - pronounced psychiatric features.

Manganese

- Dystonia
- In manganese toxicity psychiatric sign are before extrapyramidal sign .
- Less responsive to dopaminergic therapy
- MRI: Mn accumulation in GP

Carbon Monoxide

- 0.01-0.02%: headache and mild confusion.
- 0.1-0.2%: somnolence or stupor
- 1% more than 30 minutes can be fatal.

- More prolonged or severe hypoxia is accompanied by a varying combination of tremor, chorea, spasticity, dystonia, rigidity, and bradykinesia.

- Occasional patients recover completely after acute exposure only to worsen again 1-6 weeks later with acute disorientation, apathy, or psychosis
- delayed encephalopathy, parkinsonism

- Risk factors for developing this delayed encephalopathy:

✓ significant period of unconsciousness

✓ advanced age

MRI, CT: white matter, BG,GP, thalamus.

- Some residual memory deficits and parkinsonism are common.
- Nonspecific symptoms—anorexia, headache, personality changes, and memory disturbances—are attributed to carbon monoxide, but a causal relationship has not been proven.

Nitrous Oxide

- Source: Gas used in general anesthesia & Dental analgesia
- Repeated exposures are necessary to cause symptoms,

  a brief exposure to nitrous oxide,(anesthesia) is sufficient to precipitate symptoms in patients with asymptomatic B_{12} deficiency.
- Serum vitamin B_{12} and Schilling test are often normal.
- Serum homocysteine level may be elevated.
- *Myeloneuropathy* =*V*itamin B_{12} deficiency.
- Paresthesia in the hands and feet.
- Gait ataxia, sensory loss, Romberg sign.
- DTR :diminished or lost (peripheral neuropathy)
- pathologically brisk (spinal cord involvement)

Hexacarbons

- widely used volatile organic compounds employed in homes and industries as solvents and adhesives
- Toxic exposure results from inhalation, especially in poorly ventilated spaces, or excessive skin contact. .

Hexacarbons (n-Hexane and Methyl n-Butyl Ketone)

- ***Acute encephalopathy***

  euphoria, hallucination, and confusion.

- Nonspecific symptoms: insomnia and irritability, may be present.

Hexacarbons

- The most well-known syndrome:
  glue-sniffer's neuropathy
  distal symmetric sensorimotor polyneuropathy

- Early symptoms are paresthesia and sensory loss.
- Weakness involves distal muscles initially

- Proximal musculatures are affected in more severe cases.

- Easy tripping in common complain because of ankle weakness.

- Achilles stretch reflexes are lost early in the disease.

- Optic neuropathy, facial numbness, autonomic dysfunction

Hexacarbons

- Neurofilament accumulation
- Demyelination (NCV)
- CSF :Normal

Organophosphates

Pesticides and herbicides

- acute neurologic effect are muscarinic and nicotinic overactivity(hours):abdominal pain, miosis,blurred vision, muscle fasciculations, convulsion,coma muscle paralysis.
- Intermediate syndrom is result of excessive cholinergic stimulation and block of neuromuscular junction(12-96h):weakness of proximal muscle, neck flexore, cranial muscle.
- Delayed syndrom(1-4W):paresthesia,cramping pain, spasticity.

Syndrome	Neuroanatomy	Symptoms and Signs	Examples
Acute encephalopathy	Diffuse; cerebral hemispheres	headache, irritability, disorientation, convulsions, amnesia, psychosis, lethargy, stupor and coma	Acute exposure to many **toxins** at sufficient doses
Chronic encephalopathy	Diffuse; cerebral hemispheres	Cognitive and psychiatric dis-turbances	Chronic or low-dose exposure to many **toxins**
Parkinsonism	Basal ganglia & other extra-pyramidal motor pathways	Tremor, rigidity, bradykinesia, gait instability	**Mn, CO, Methanol**
Motor neuron disease	Spinal cord motor neurons	Muscle atrophy, weakness	**Lead, manganese**
Myeloneuropathy (myelopathy & polyneuropathy)	Spinal cord & peripheral nerves	Paresthesias, sensory loss, hyperreflexia, Babinski sign,	**NO, organophosphates, n-hexane**
Polyneuropathy	Peripheral sensory, motor & autonomic nerve fibers	Paresthesias, numbness, weakness, loss of DTR, autonomic failure	Many **toxins** at sufficient doses

Toxic polyneuropathies

Mostly sensory or sensorimotor polyneuropathy (little or no weakness)

- Acrylamide
- Carbon disulfide
- Ethylene oxide
- Metals: arsenic, lead, mercury, thallium
- Methyl bromide

Acrylamid

- workers who handle monomeric acrylamide in the production of polyacrylamides
- workers exposed to monomeric acrylamide used in grouting
- Papermaking workers, soil-stabilization workers, textile workers, tunnel workers, and well drillers.

Acrylamid

Features of poisoning include:

- local skin irritation
- weight loss
- lassitude
- Neurologic symptoms of central and peripheral nervous system involvement.

Acrylamid

- Acute exposure typically causes a confusional state, (disorientation, memory loss, and gait ataxia). These symptoms are largely reversible
- Both sensory and motor nerves are affected

sensory loss, weakness, ataxia, and loss of tendon reflexes.

The loss of reflexes especially may be generalized, unlike other toxic neuropathies, in which only distal reflexes are lost.

Autonomic involvement (hyperhidrosis and urinary retention) is common.

- *Predominantly motor polyneuropathy or sensori-motor polyneuropathy with significant weakness:*

- Hexacarbons: n-hexane, methyl n-butyl ketone
- Metals: lead, arsenic, mercury
- Organophosphates

Cranial neuropathy:

- Thallium
- Trichloroethylene (trigeminal neuropathy)

Purely sensory neuropathy (disabling sensory loss with no weakness):

- cis-platinum
- Pyridoxine abuse

Prominent autonomic dysfunction:

- Acrylamide
- n-Hexane (glue-sniffer)
- Thallium

NEUROBEHAVIOURAL TESTS

USED IN

NEUROTOXICITY ASSESSMENTS

Neurobehavioral core test battery(NCTB)

- The test series assesses the following functions:

  Affect, attention, response speed, auditory memory, manual dexterity, perceptual motor speed, visual perception, motor steadiness

WHO NCTB

	Test	Functional Domain Test
mood	***Profile of mood state***	Affect
cognitive	***Digit Symbol***	Perceptual-motor speed
	Digit span	Auditory memory
	Benton visual retention	Visual perception/memory
Motor	***Aiming***	Motor steadiness
motor	***Simple reaction time***	Attention/response speed
	Santa Ana dexterity	Manual dexterity

ATTENTION AND MEMORY

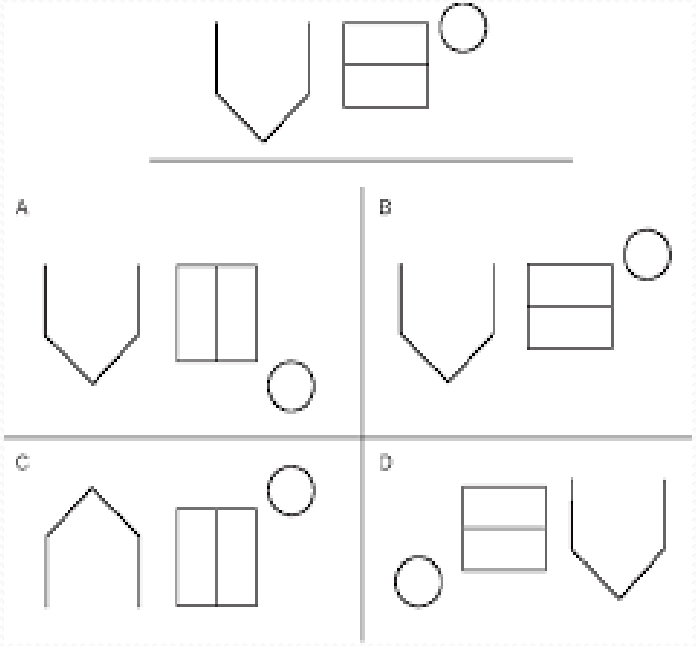
- The *Digit Span* subtest of the WAIS is the most frequently used test of attention and memory.

- In the *Benton Visual Retention Test*, groups of symbols (e.g., triangles, squares) are shown to participants who are then asked to select from four similar groupings that are identical to the initial grouping

Digit Span

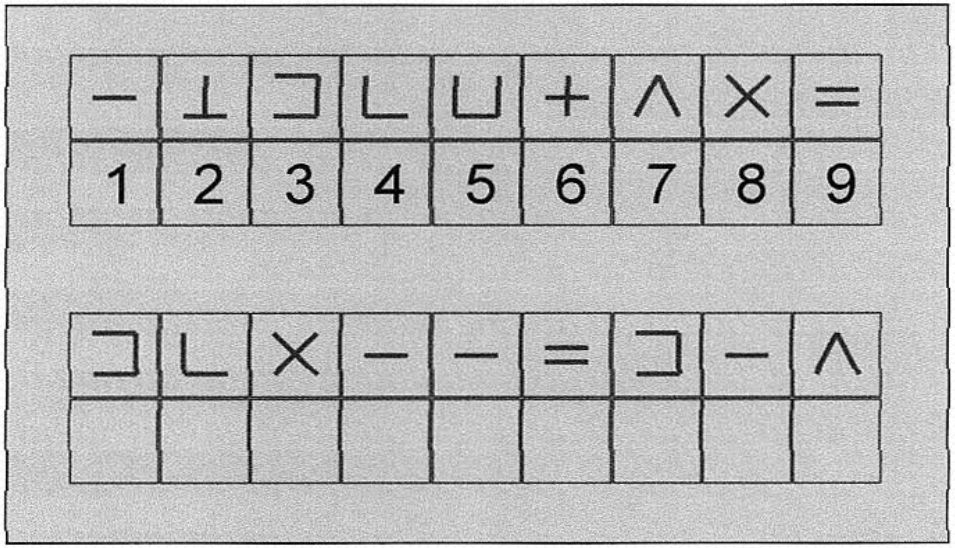
Forward digit span task		Backward digit span task	
(1)	5 · 8 · 2	(1)	2 · 4
	6 · 9 · 4		5 · 8
(2)	6 · 4 · 3 · 9	(2)	6 · 2 · 9
	7 · 2 · 8 · 6		4 · 1 · 5
(3)	4 · 2 · 7 · 3 · 1	(3)	3 · 2 · 7 · 9
	7 · 5 · 8 · 3 · 6		4 · 9 · 6 · 8
(4)	6 · 1 · 9 · 4 · 7 · 3	(4)	1 · 5 · 2 · 8 · 6
	3 · 9 · 2 · 4 · 8 · 7		6 · 1 · 8 · 4 · 3
(5)	5 · 9 · 1 · 7 · 4 · 2 · 8	(5)	5 · 3 · 9 · 4 · 1 · 8
	4 · 1 · 7 · 9 · 3 · 8 · 6		7 · 2 · 4 · 8 · 5 · 6
(6)	5 · 8 · 1 · 9 · 2 · 6 · 4 · 7	(6)	8 · 1 · 2 · 9 · 3 · 6 · 5
	3 · 8 · 2 · 9 · 5 · 1 · 7 · 4		4 · 7 · 3 · 9 · 1 · 2 · 8
(7)	2 · 7 · 5 · 8 · 6 · 2 · 5 · 8 · 4	(7)	9 · 4 · 3 · 7 · 6 · 2 · 5 · 8
	7 · 1 · 3 · 9 · 4 · 2 · 5 · 6 · 8		7 · 2 · 8 · 1 · 9 · 6 · 5 · 3

Benton Visual Retention Test



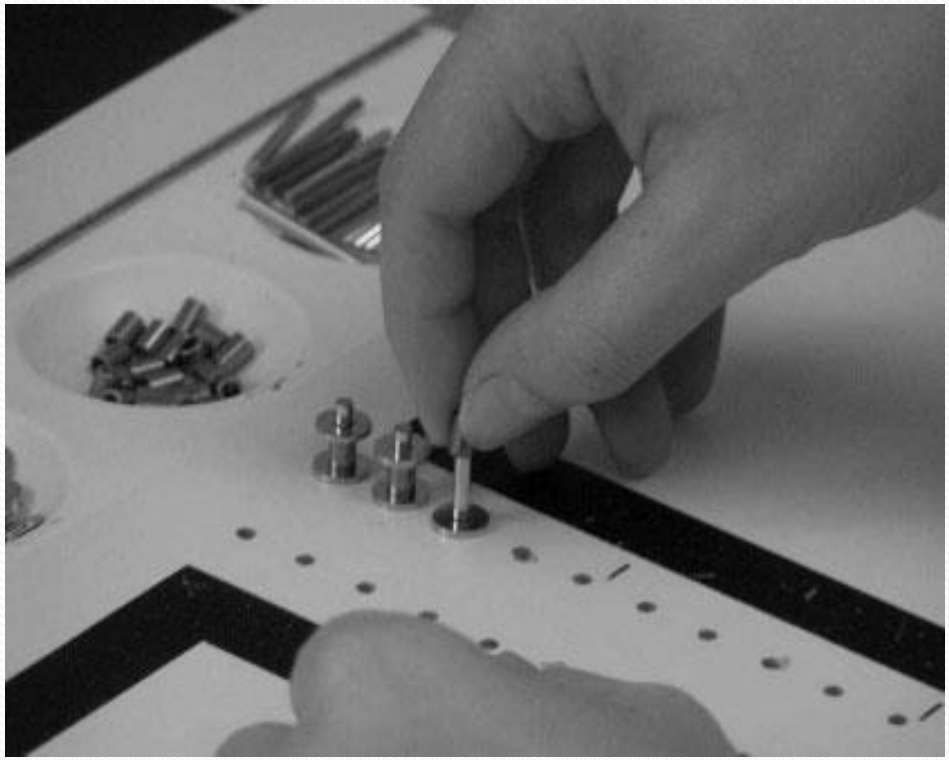
CODING

- *Digit Symbol*
- The Digit Symbol is among the widest range of neuropsychological functions of any test used in this field of research and is among the most sensitive to neurotoxicants.



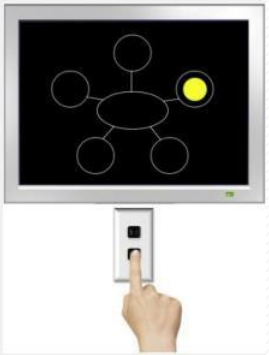
❖ Peg board

Measure rapid eye-hand coordinated movement



Simple Reaction Time

Simple Reaction Time (SRT) is a test which measures simple reaction time through delivery of a known stimulus to a known location to elicit a known response. The only uncertainty is with regard to when the stimulus will occur, by having a variable interval between the trial response and the onset of the stimulus for the next trial. As soon as the participant sees the square on the screen, they must press the button on the press pad.



PSYCHOSOCIAL TESTS

- Psychosocial tests assess such aspects of human functioning as personality, mood, attitudes, and psychiatric symptoms.

- *Profile of Mood States test*

- These questionnaires have been useful in distinguishing between exposed and unexposed populations

THE END