CMU

CENTRAL MICHIGAN UNIVERSITY

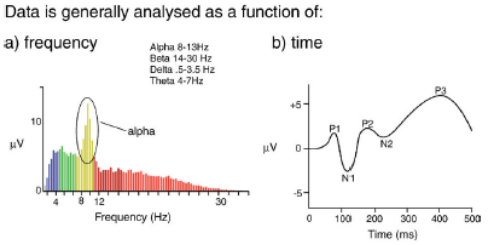

Fig. 1 – Brief summary of EEG and ERP measurement and analyses. For a more detailed introduction to electrophysiology, see Luck, 2005.

FNI

Electrodiagnostic Correlates of Neurodegenerative Diseases

Michigan Society of Electrodiagnostic Technologists

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Outline of Presentation

- Pre-test
- Goals of Presentation
- Neurophysiology Basics
- Neurodegenerative Diseases & Electrodiagnostics
    - --Alzheimer's disease
    - --Parkinson's disease
    - --Huntington's disease
    - --Multiple Sclerosis
    - --Amyotrophic Lateral Sclerosis
- Summary
- Post-test
- Questions

Pre-Test

1. A critical receptor type for mediating LTP is the:

   a. D2 b. NMDA c. GluR2 d. D4

2. Increases in which band frequency is most commonly associated with severe Alzheimer's:

   a. 2-5 Hz b. 7-11 Hz c. 14-18 Hz d. 20-24 Hz

3. A common DBS target for PD patients is the:

   a. CN b. SNc c. SNr d. STN

4. Which of the following is suppressed in HD:

   a. alpha b. beta c. theta d. delta

5. A delay in VEP is seen often in patients with:

   a. AD b. PD c. HD d. MS

Goals of Presentation

- **Provide overview of how electrodiagnostic techniques will be useful in diagnosing, monitoring, and treating a variety of neurodegenerative disorders**
- **Provide a review of basic neurophysiology in the context of understanding dynamics of five types of neurodegenerative diseases**
- **Explore ways in which electroneurodiagnostics can further our understanding of neurodegenerative diseases**

Neurophysiology Basics

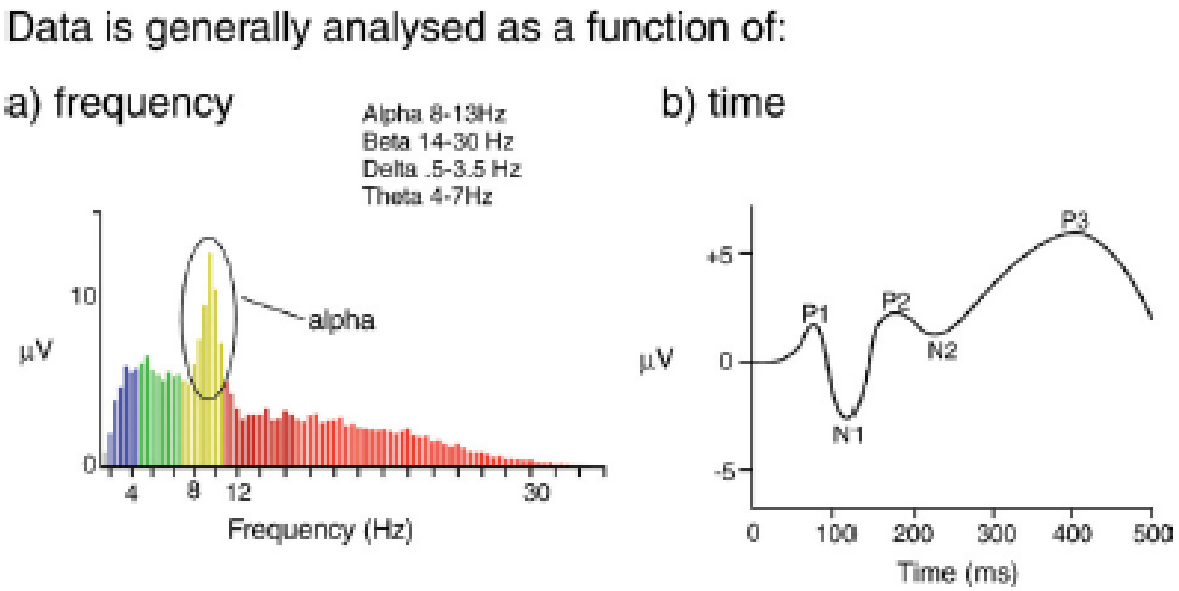
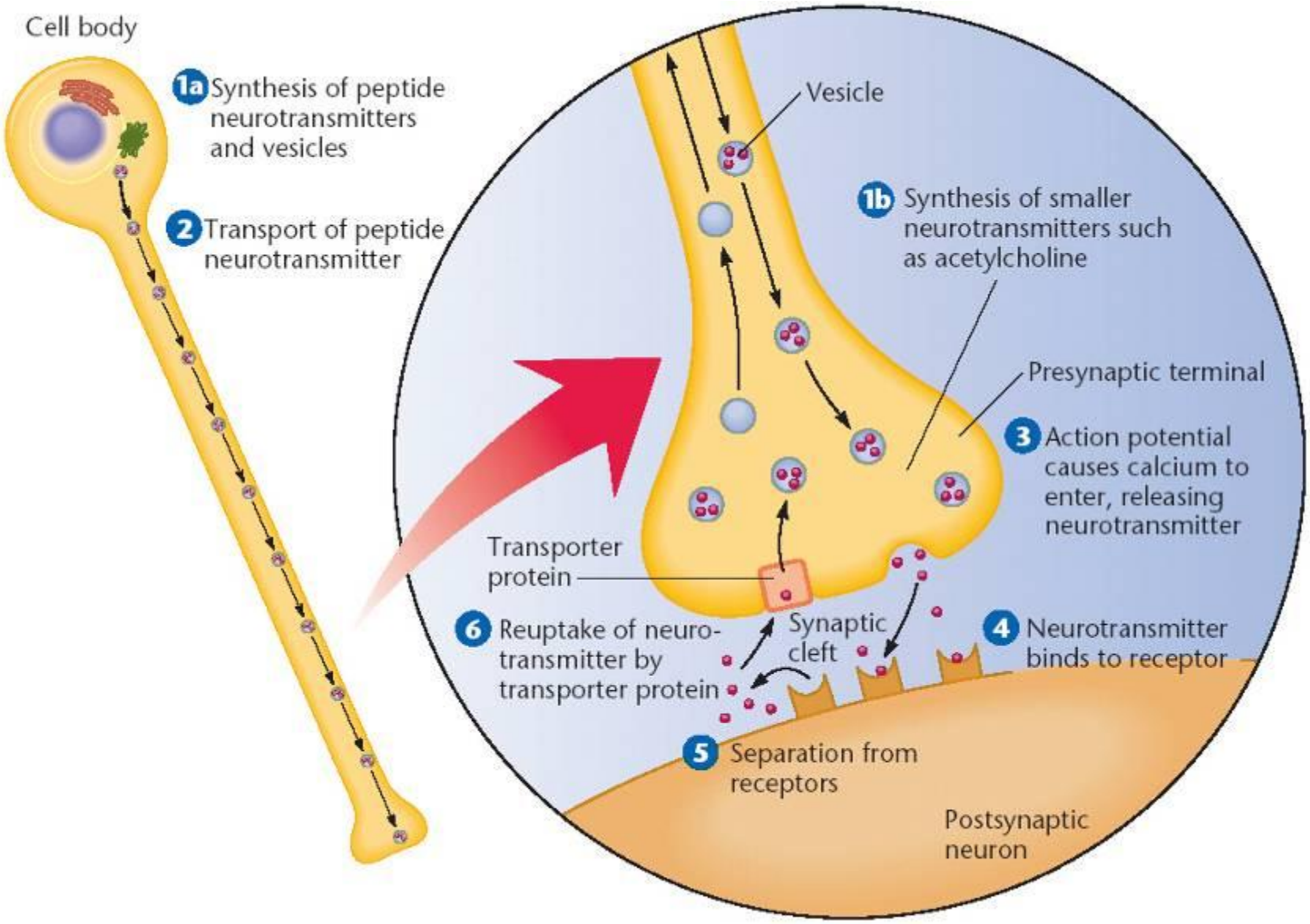


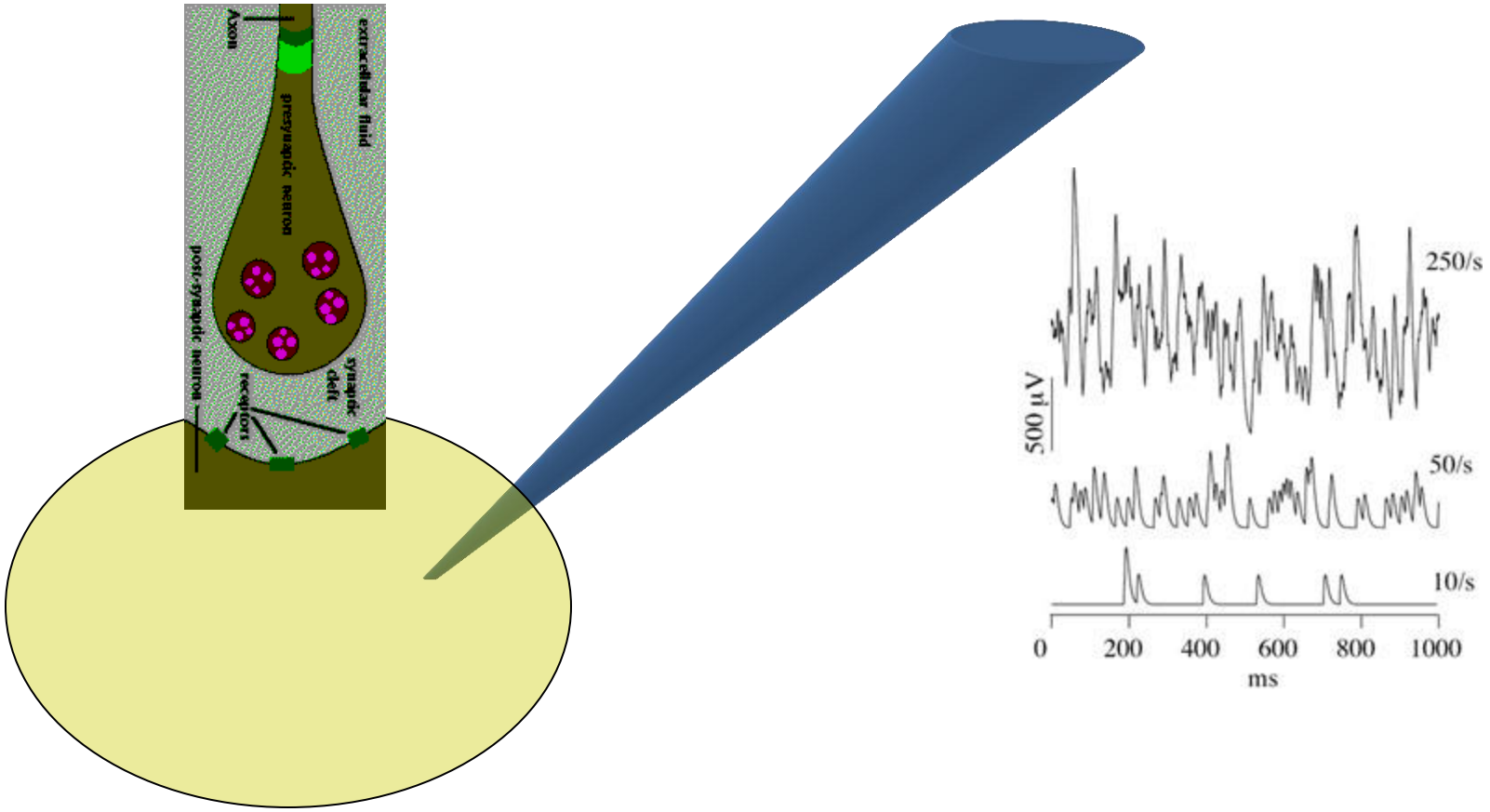
Fig. 1 – Brief summary of EEG and ERP measurement and analyses. For a more detailed introduction to electrophysiology, see Luck, 2005.

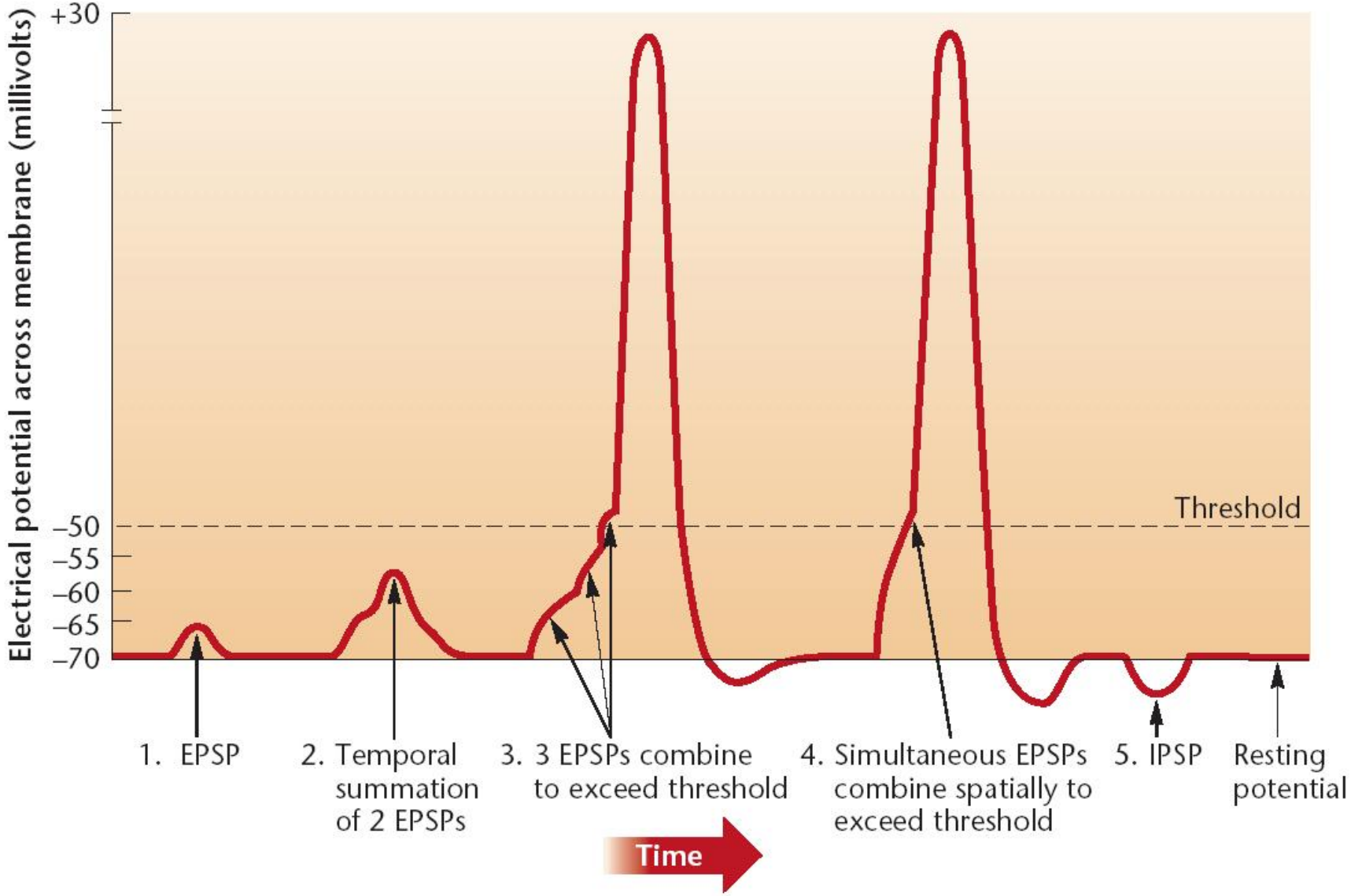

Cell body
1a Synthesis of peptide neurotransmitters and vesicles
2 Transport of peptide neurotransmitter
Vesicle
1b Synthesis of smaller neurotransmitters such as acetylcholine
Presynaptic terminal
3 Action potential causes calcium to enter, releasing neurotransmitter
Transporter protein
6 Reuptake of neuro-transmitter by transporter protein
Synaptic cleft
4 Neurotransmitter binds to receptor
5 Separation from receptors
Postsynaptic neuron

Postsynaptic Potentials

- **EPSP**: Excitatory Post Synaptic potential
  - Neurotransmitter causes local, graded depolarization on the postsynaptic neuron
- **IPSP**: Inhibitory Post Synaptic Potential
  - Neurotransmitter causes local, graded hyperpolarization on the postsynaptic neuron
- **Quanta**: the amount of neurotransmitter stored in a single synaptic vesicle, thus the lowest level potential postsynaptic effect

Intracellular Recording can measure Quanta




Electrical potential across membrane (millivolts)
+30
–50
–55
–60
–65
–70
Threshold
1. EPSP
2. Temporal summation of 2 EPSPs
3. 3 EPSPs combine to exceed threshold
4. Simultaneous EPSPs combine spatially to exceed threshold
5. IPSP
Resting potential
Time

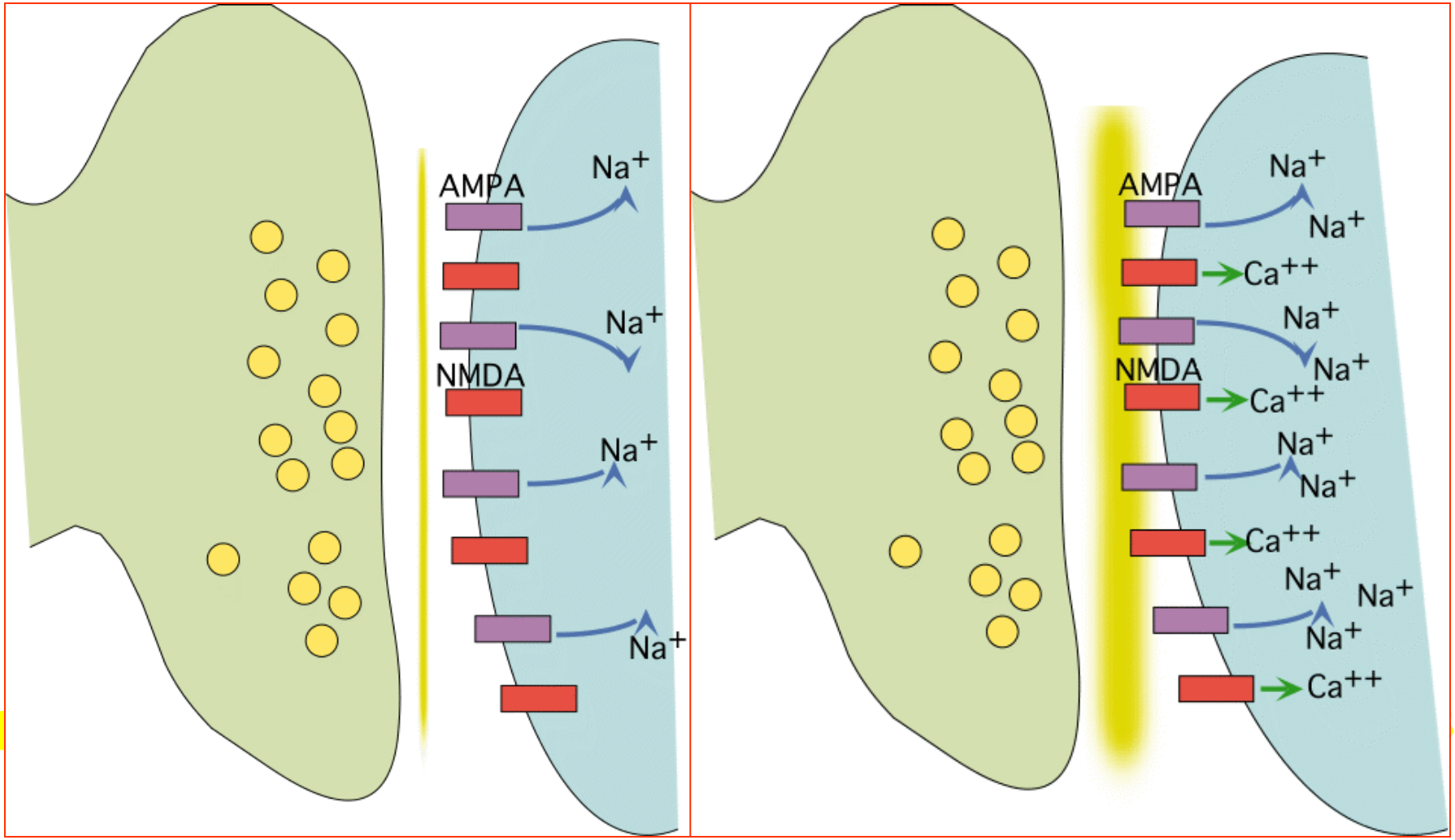
Ways cell A could stimulate cell B more effectively

1. Cell A could release more neurotransmitter
   - Cell A could increase synaptic vesicles released or transmitter contained in vesicles
   - Cell A could increase number of axon terminals that synapse with cell B
2. Cell B could become more sensitive
   - Cell B could decrease dendritic spine length
   - Cell B could increase number of receptors
   - Cell B could increase sensitivity of receptors

Mechanism of LTP

- Glutamate activates AMPA receptors and depolarizes membrane causing release of magnesium from NMDA receptor.
- Sodium and calcium rush in NMDA receptor and calcium activates CaMKII, which increases dendritic branching.
- Retrograde transmitters causes increase production of GAP-43 in presynaptic cell, leading to axonal growth

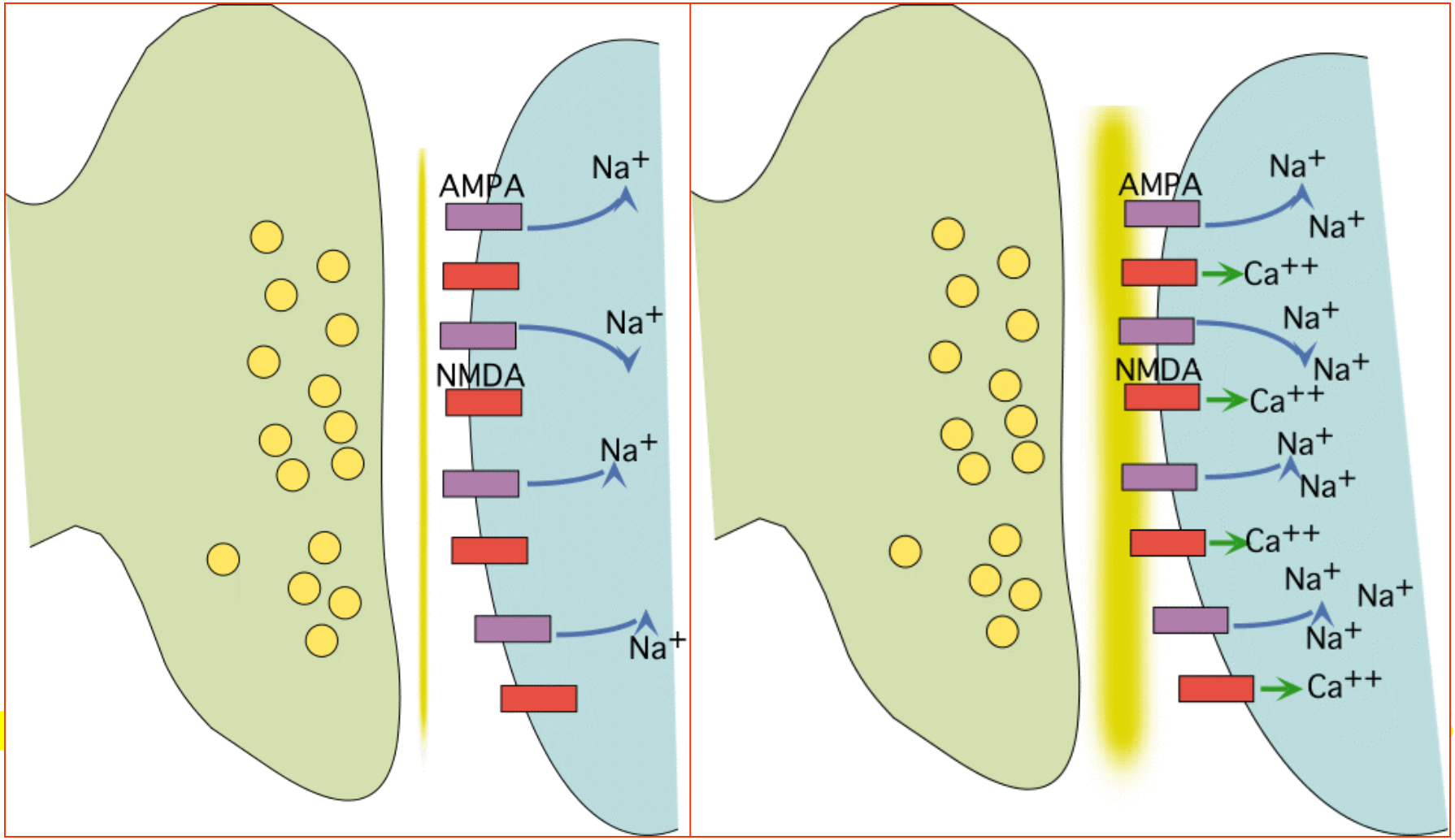
LTP and the NMDA Receptor



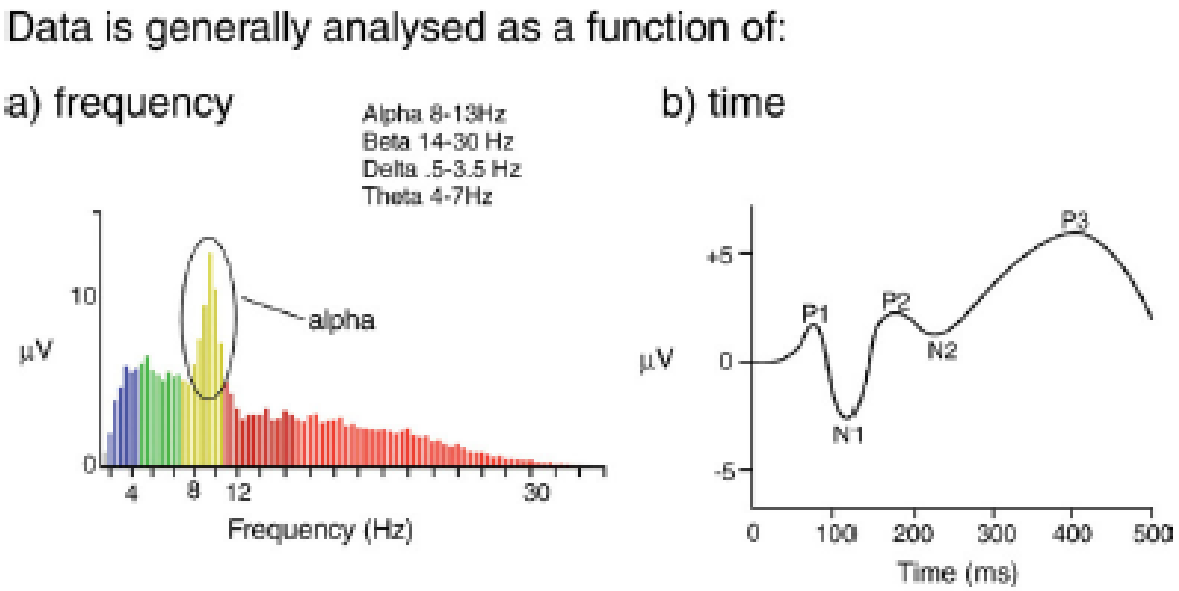
After Ca^{2+}, CAMKII

- Calcium calmodulin kinase II linked to…
  - Phosphorylation of AMPA receptors, increasing their sensitivity
  - Increased numbers and strategic placement of AMPA receptors
  - “Silent” (unresponsive) AMPA receptors becoming active
  - Branching of dendrites (additional synapses with same axon)

LTP and the NMDA Receptor



Neurodegenerative Diseases and Electrodiagnostics



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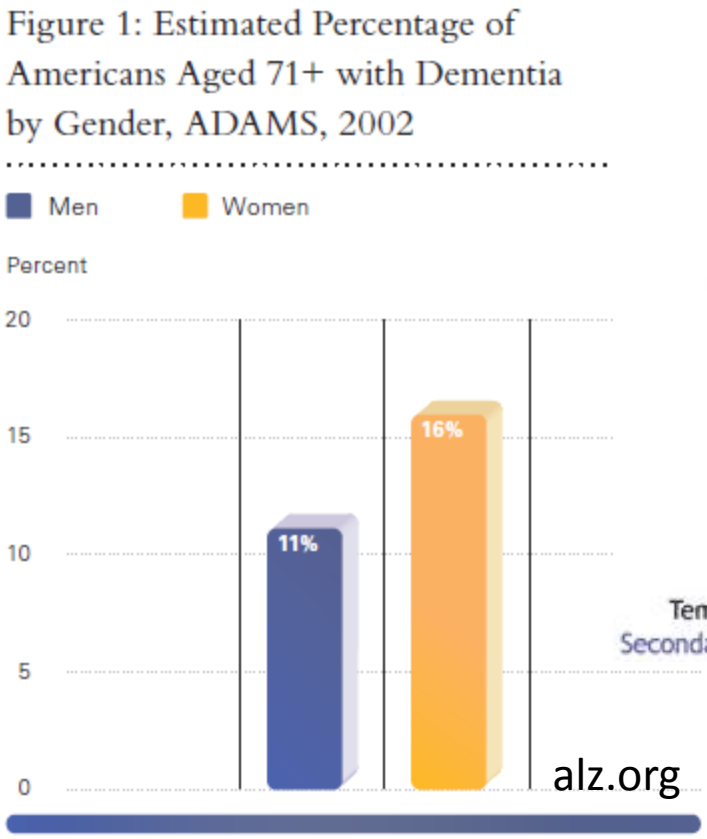
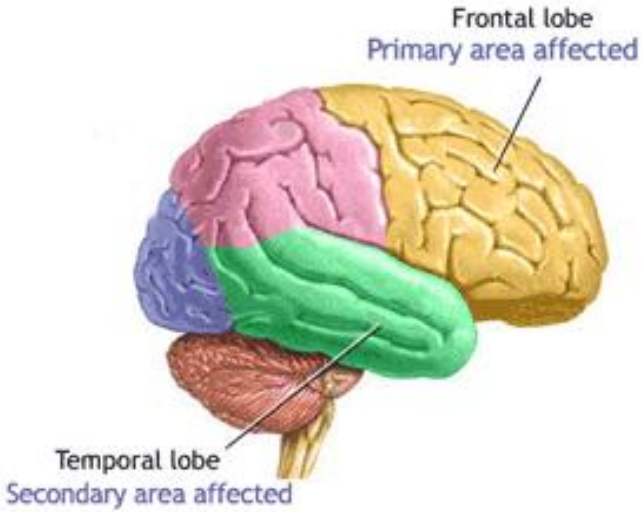
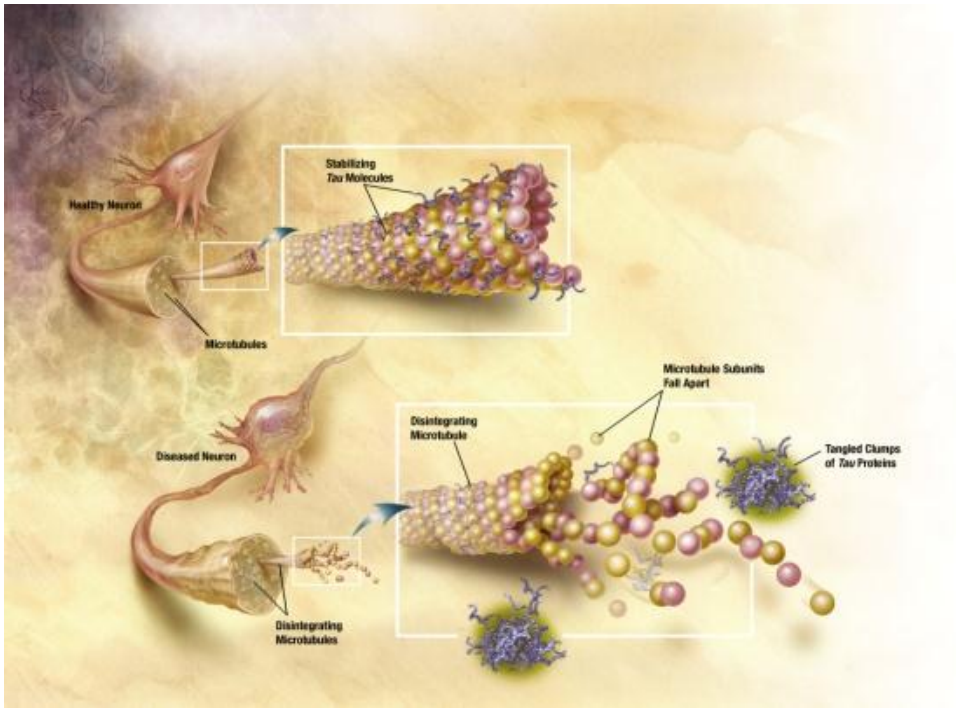
Alzheimer's disease

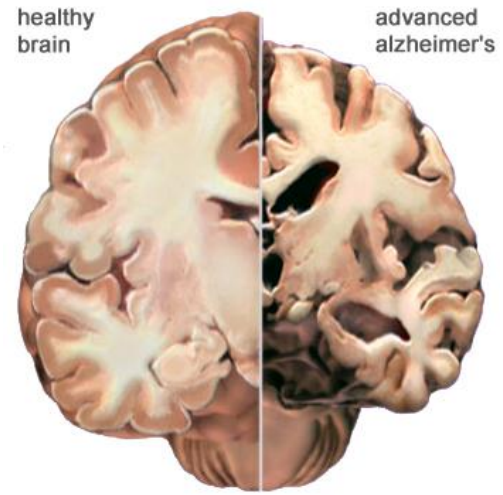


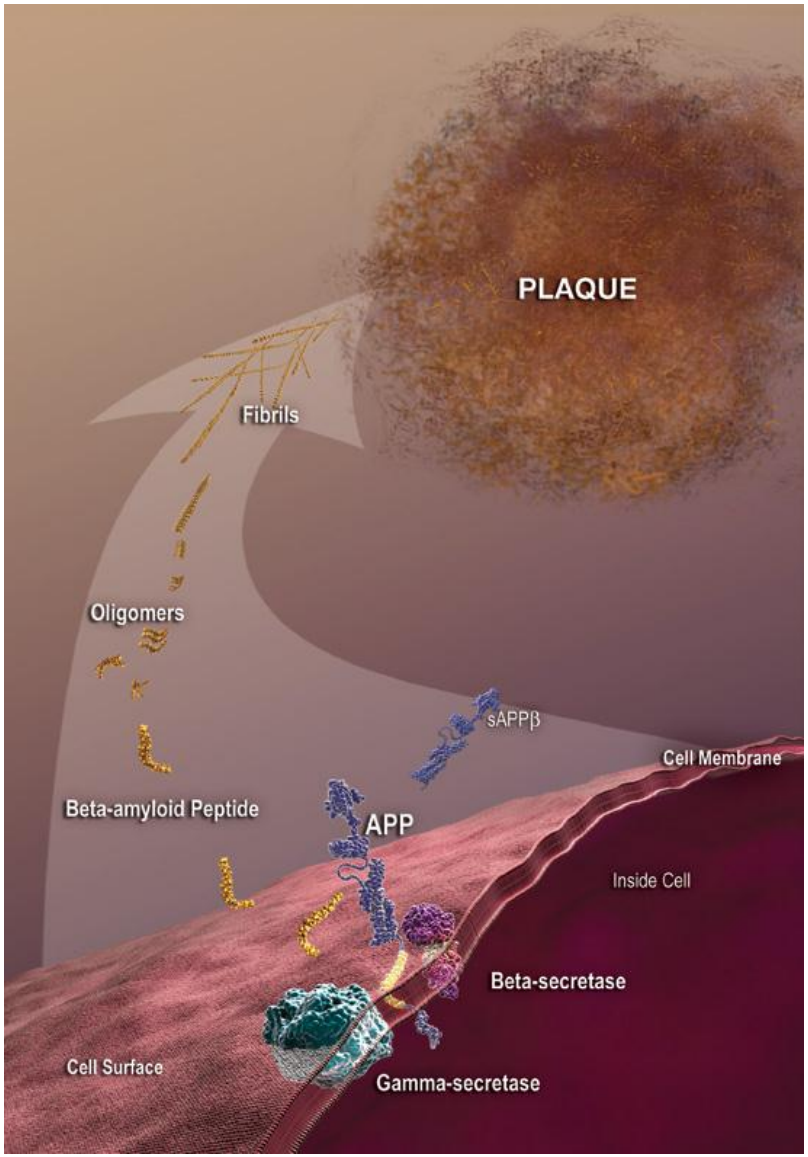


- Effects over 5.3 million Americans
- 5th leading cause of death in those >65
- $183 billion in health care costs
- High emotional and physical stress to unpaid care givers

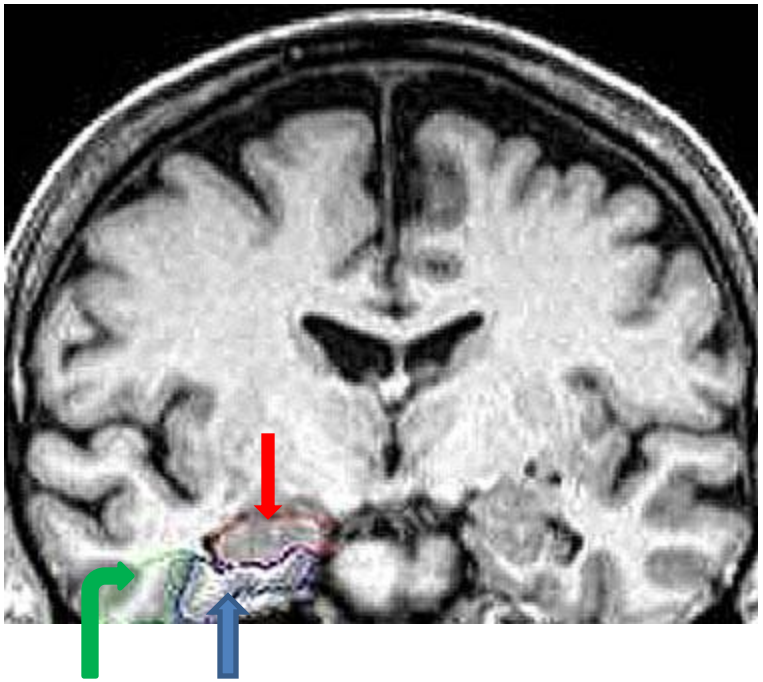
Two Major Hallmarks



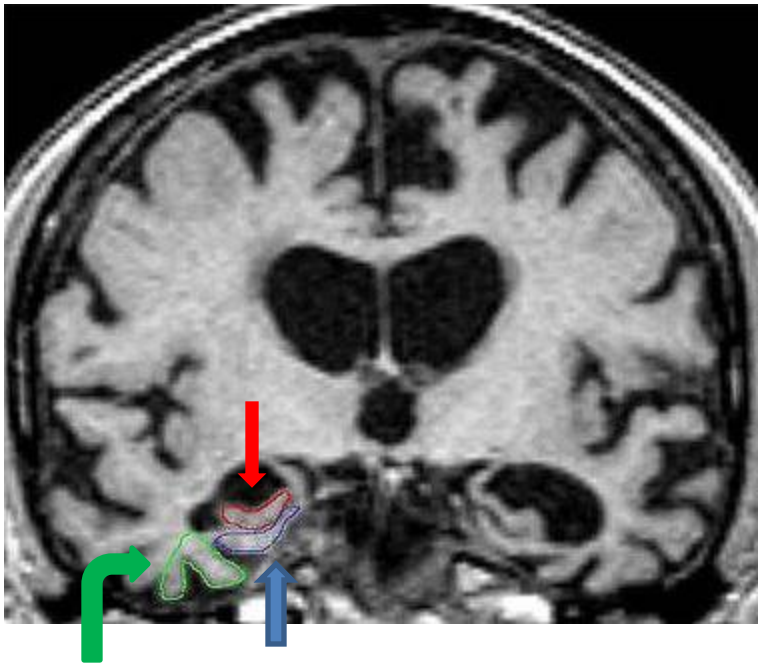




AD Atrophy



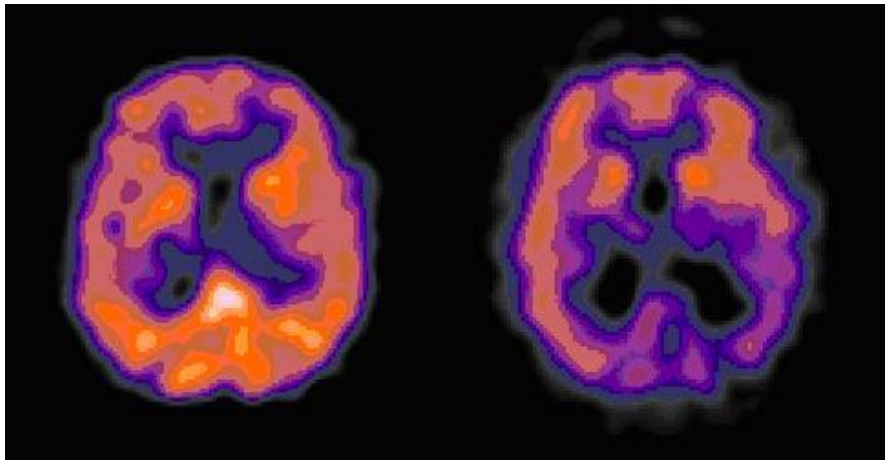
Normal Brain



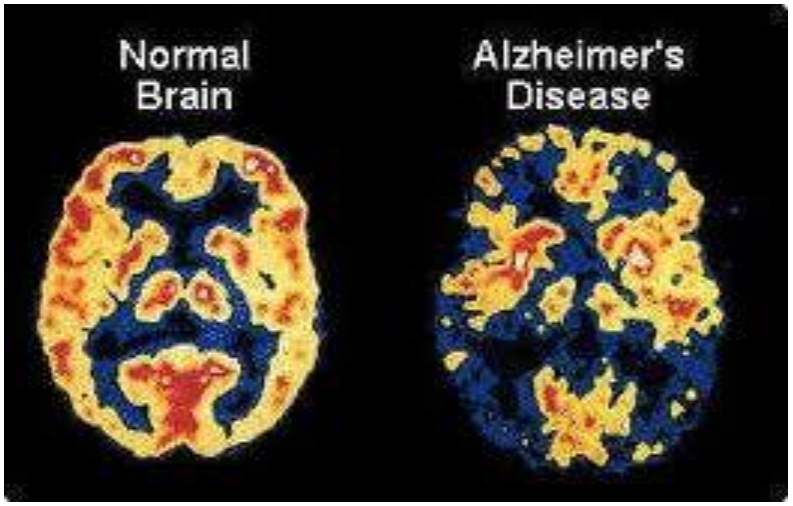
Alzheimer's Brain

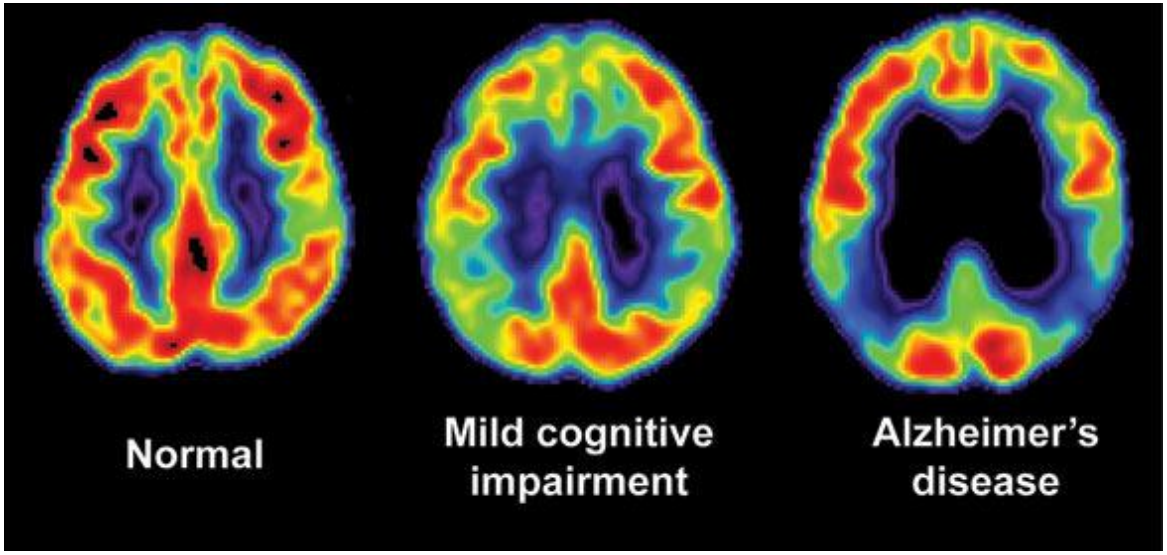
Hippocampus Entorhinal cortex Perirhinal cortex

fMRI and MRI of Healthy and AD Brain



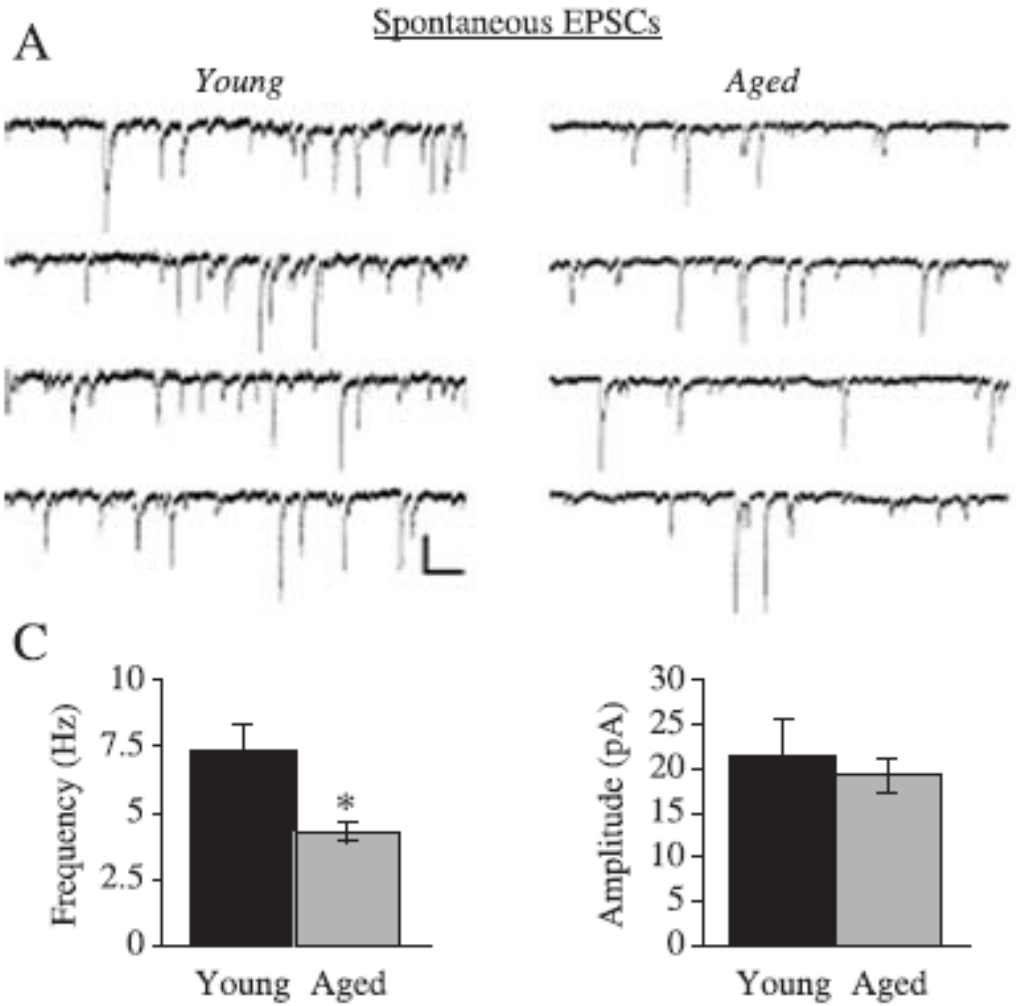
Healthy **AD**





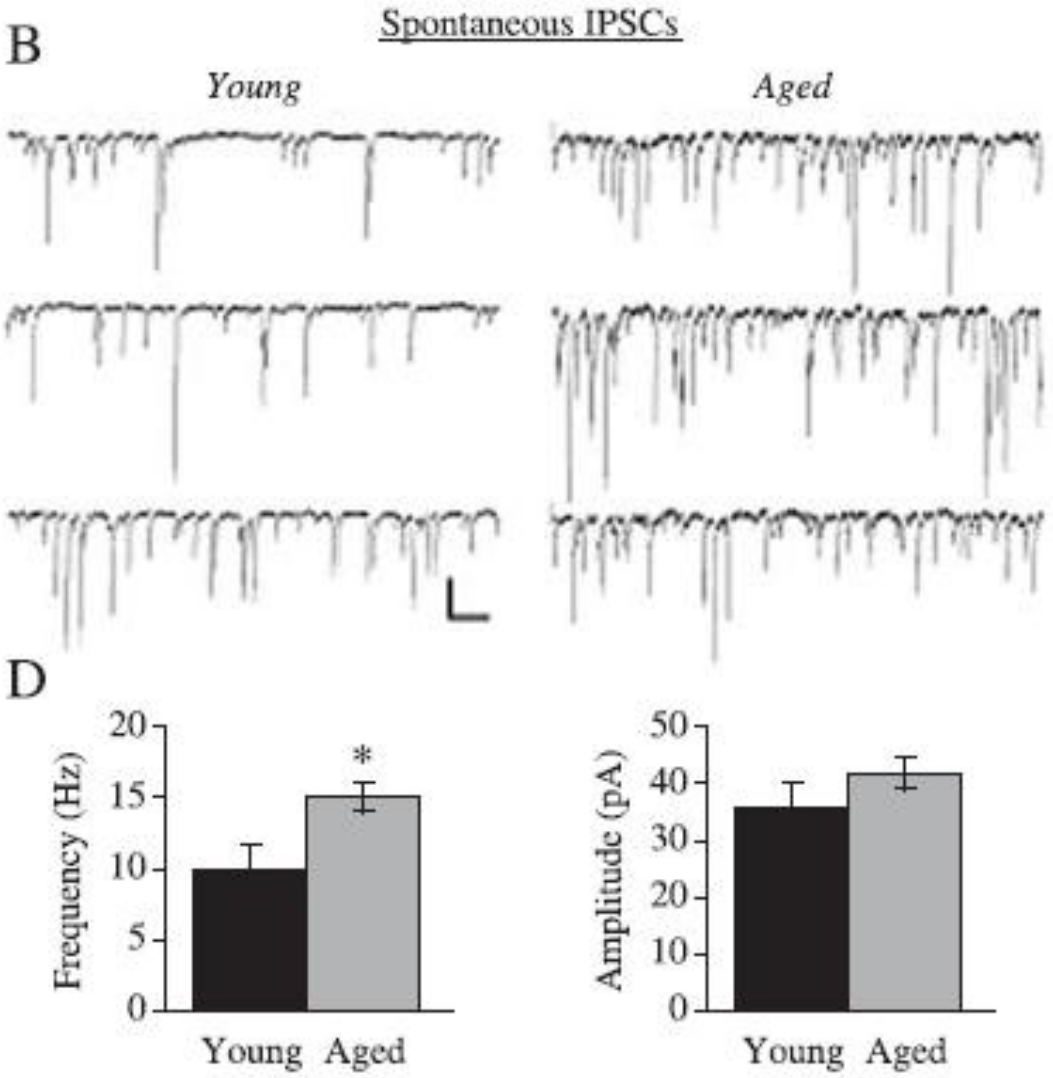
Monkey Studies with Electrophysiology

Frequency of excitatory post-synaptic currents decreased in the aged monkey prefrontal cortex (Luebke et al 2004)



Monkey Studies with Electrophysiology

Frequency of inhibitory post synaptic currents decreased in the aged monkey prefrontal cortex (Luebke et al 2004).



EEG for Severity of AD

Guido Rodriguez et al 2011

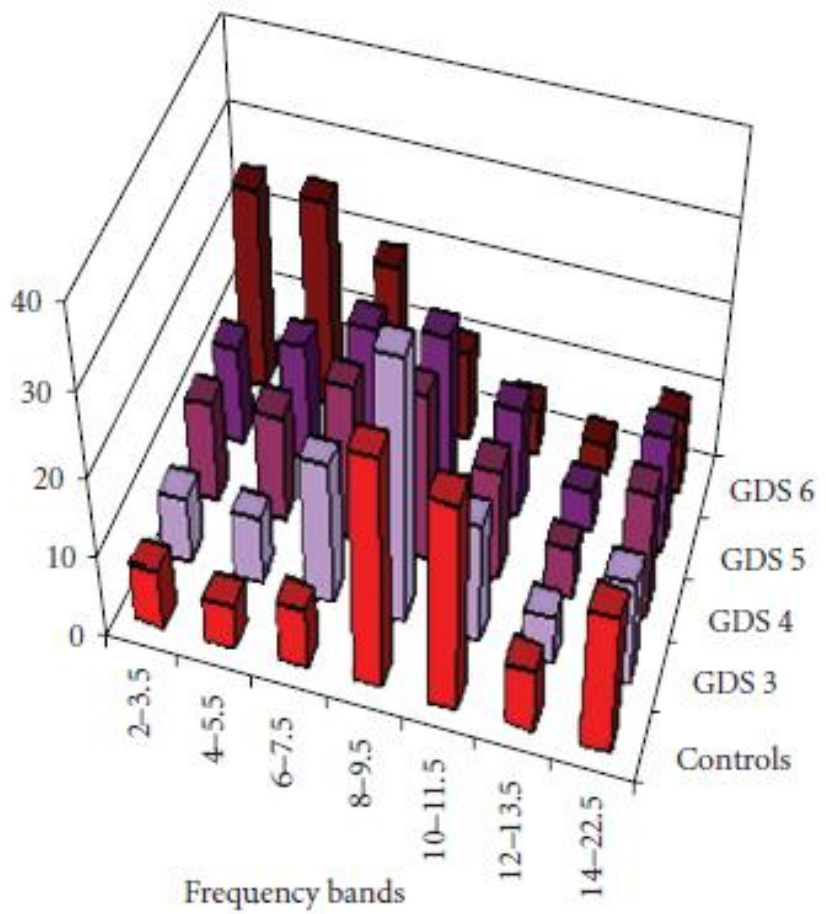
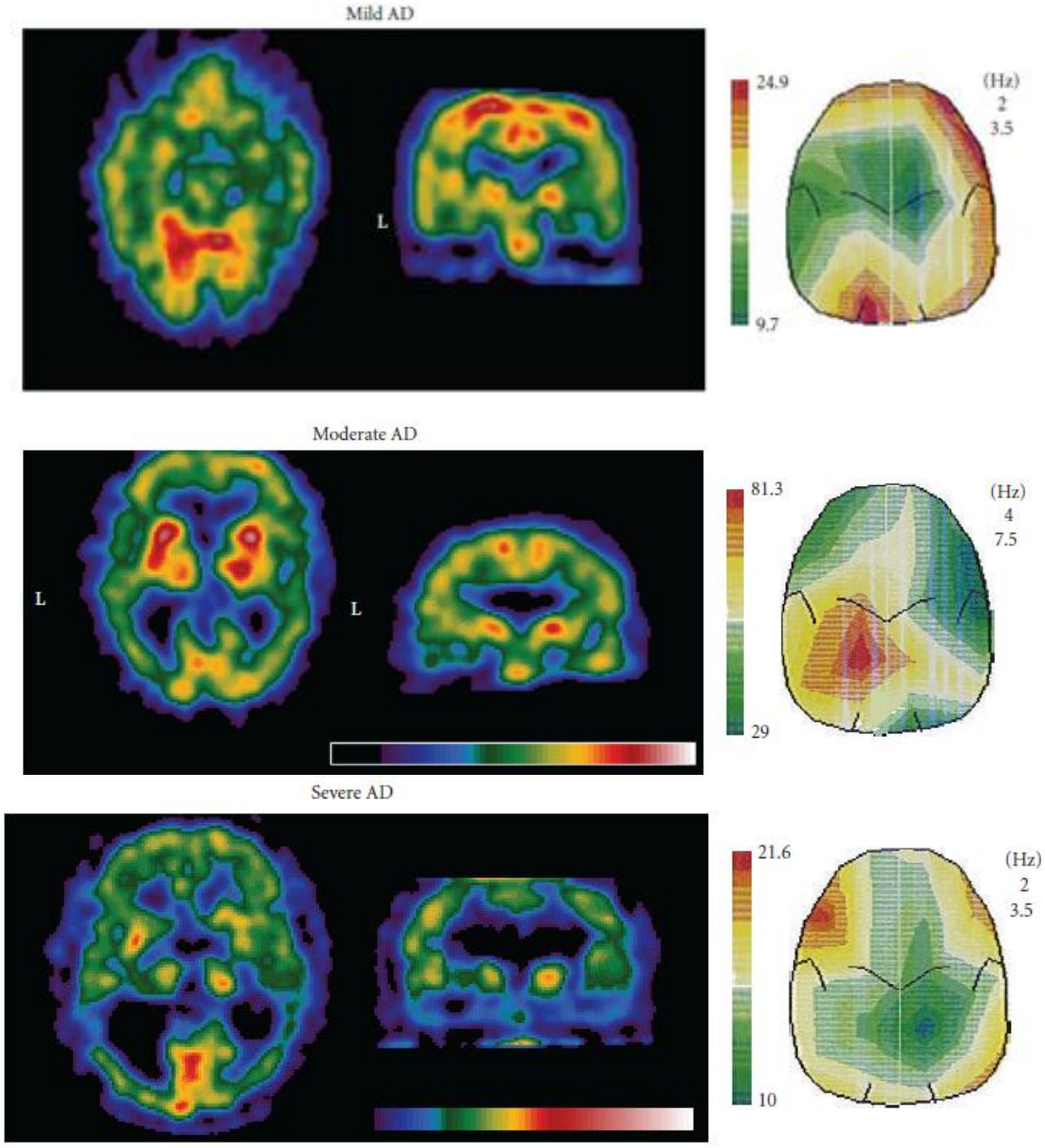


FIGURE 2: Histogram showing the relationship between 7 EEG frequency bands (2–3.5; 4–5.5; 6–7.5; 8–9.5; 10–11.5; 12–13.5;14–22.5 Hz) and disease's severity (normal controls and 4 clinical classes of severity; GDS 3 to 6).

SPECT and EEG in AD

Guido Rodriguez et al 2011



Parkinson's disease

Definitions

Progressive and continuous neurodegenerative disorder

First symptoms after 55 years old

No restorative treatments

Symptoms :

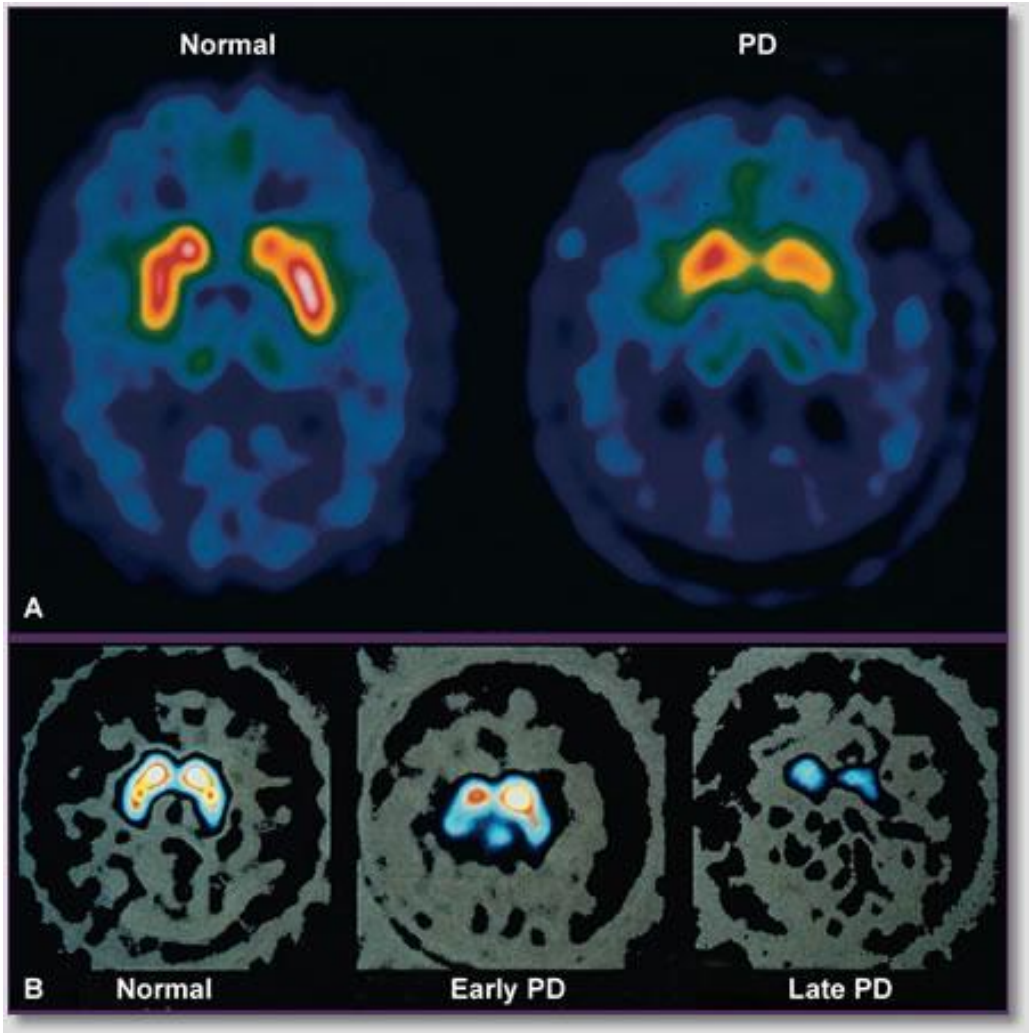
Slowing of physical movements (bradykinesia and akinesia)

Muscular rigidity

Tremors

Postural instability

PET and SPECT



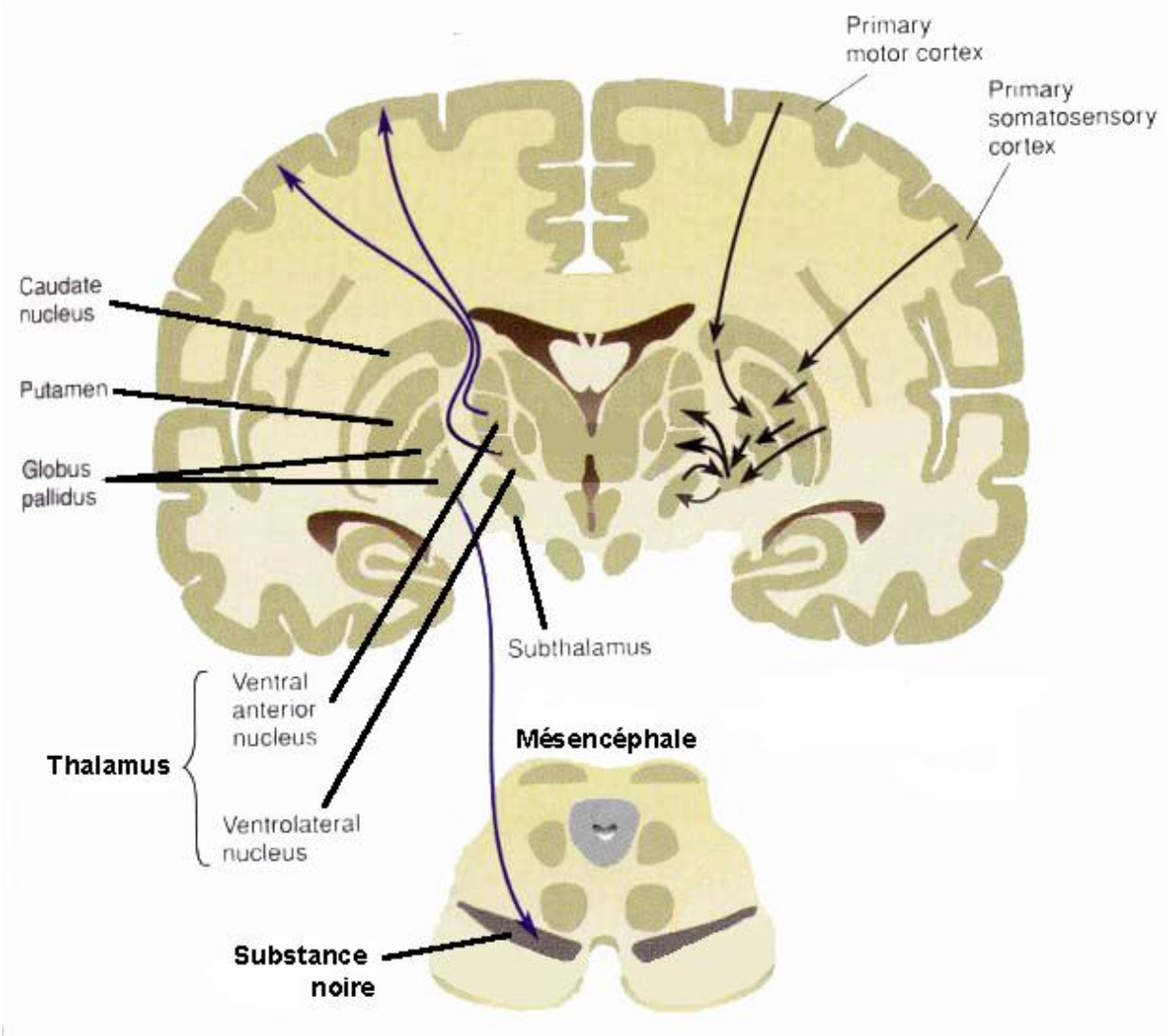
PET

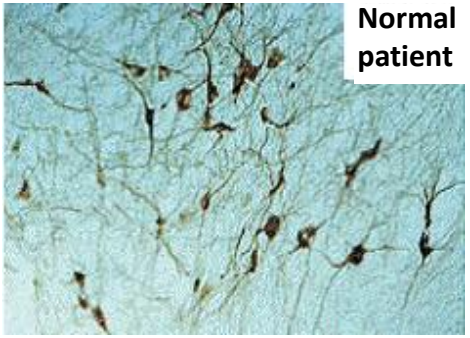
SPECT

[18F]dopa PET and β-CIT SPECT images. [18F]dopa PET uptake in the putamen is reduced in patients with PD compared with normal controls (A). Reduction in β-CIT SPECT uptake in the putamen correlates with the severity of PD (B)

Parkinson's disease

Loss of dopaminergic neurons in the substantia nigra





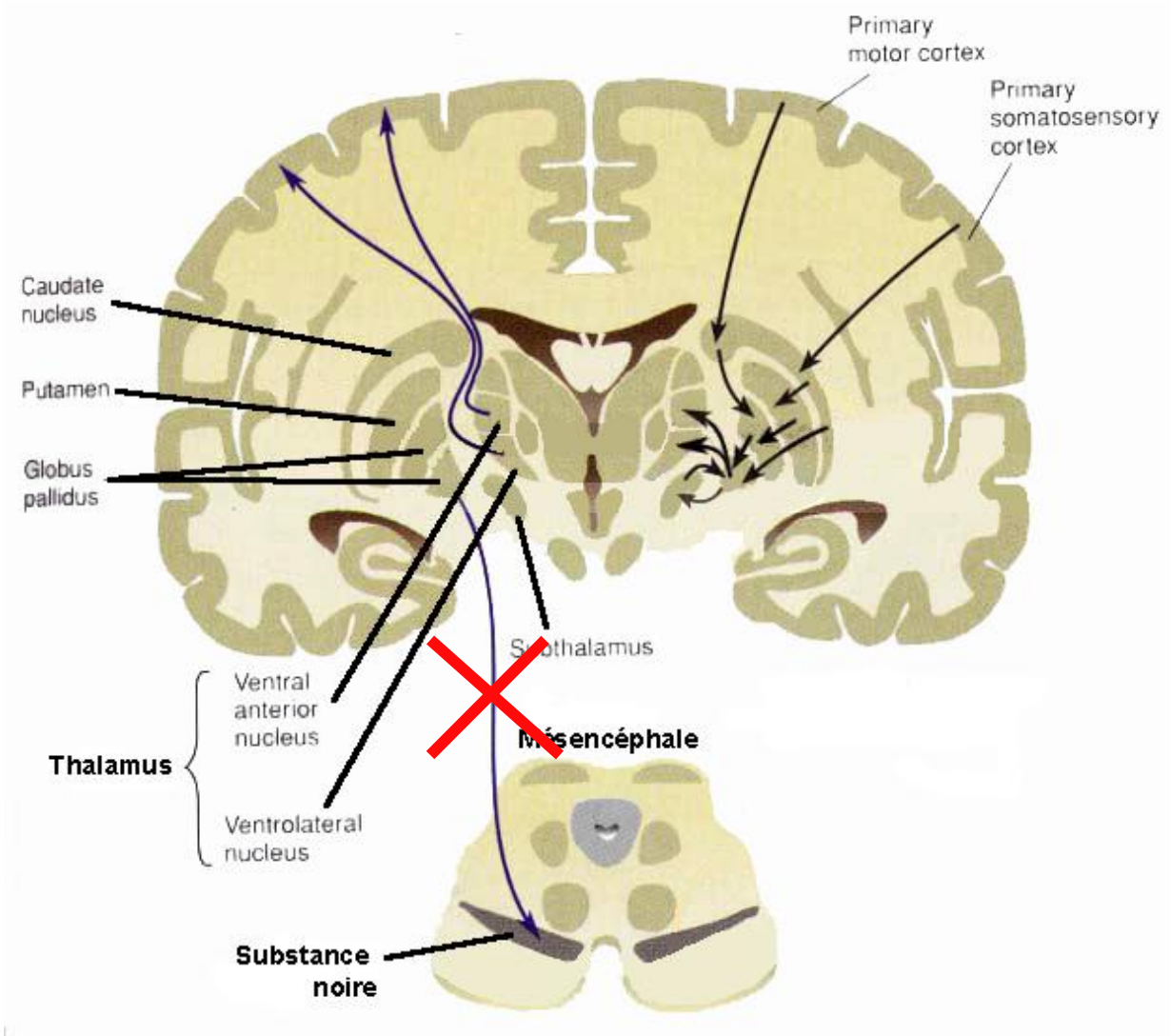
Normal patient

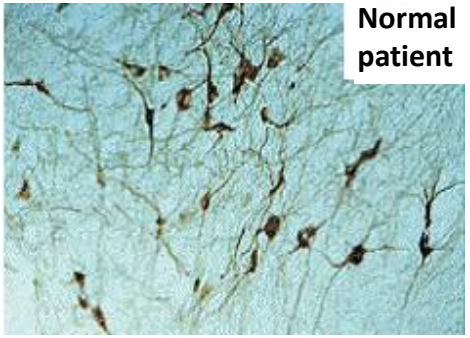
Parkinsonian patient

Parkinson's disease

Loss of dopaminergic neurons in the substantia nigra

➡ Loss of the nigro-striatal pathway

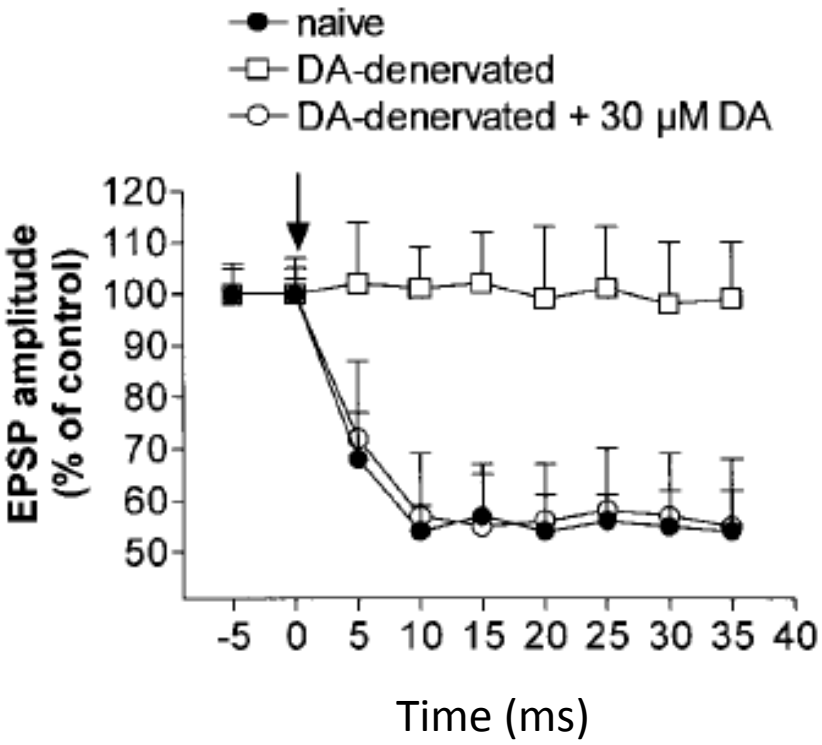


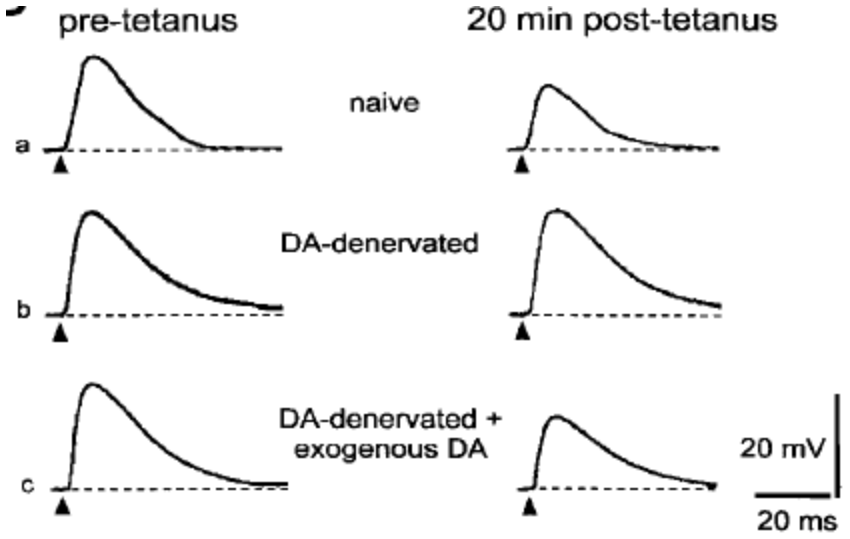


Normal patient

Parkinsonian patient

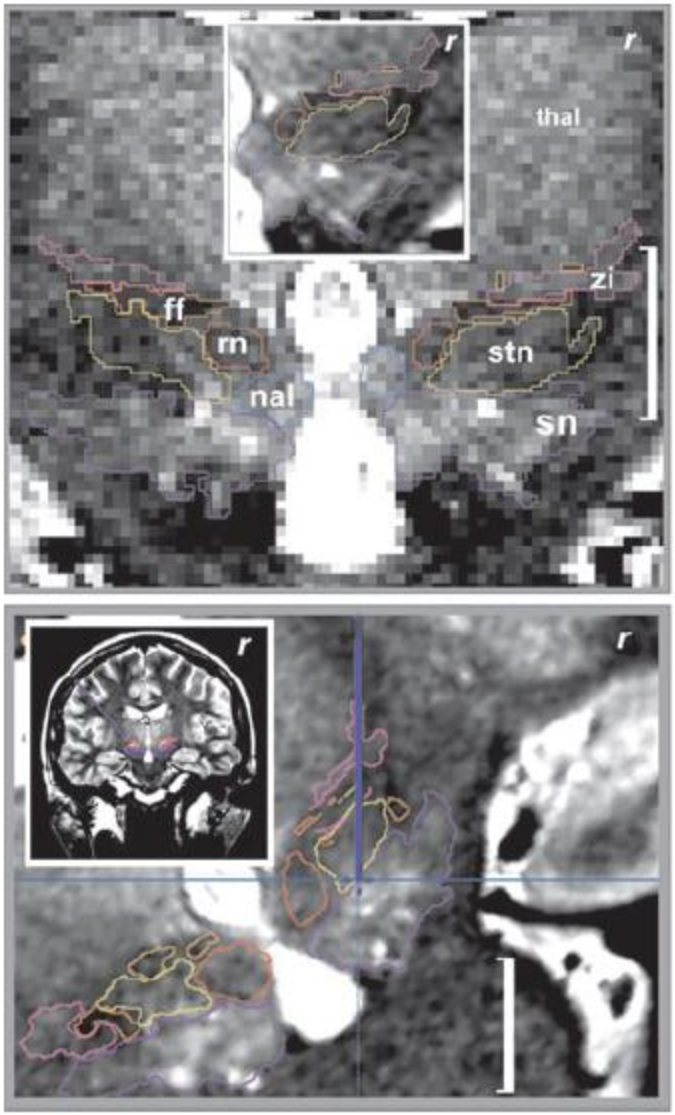
LTD and Parkinson's disease

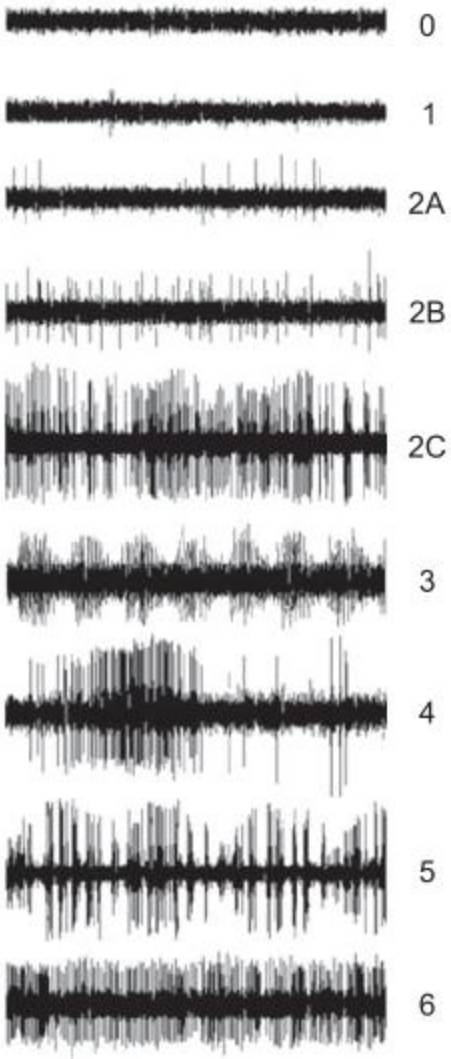




Dopamine (DA)-denervation prevents cortico-striatal long term depression

EEG for Deep Brain Stimulation

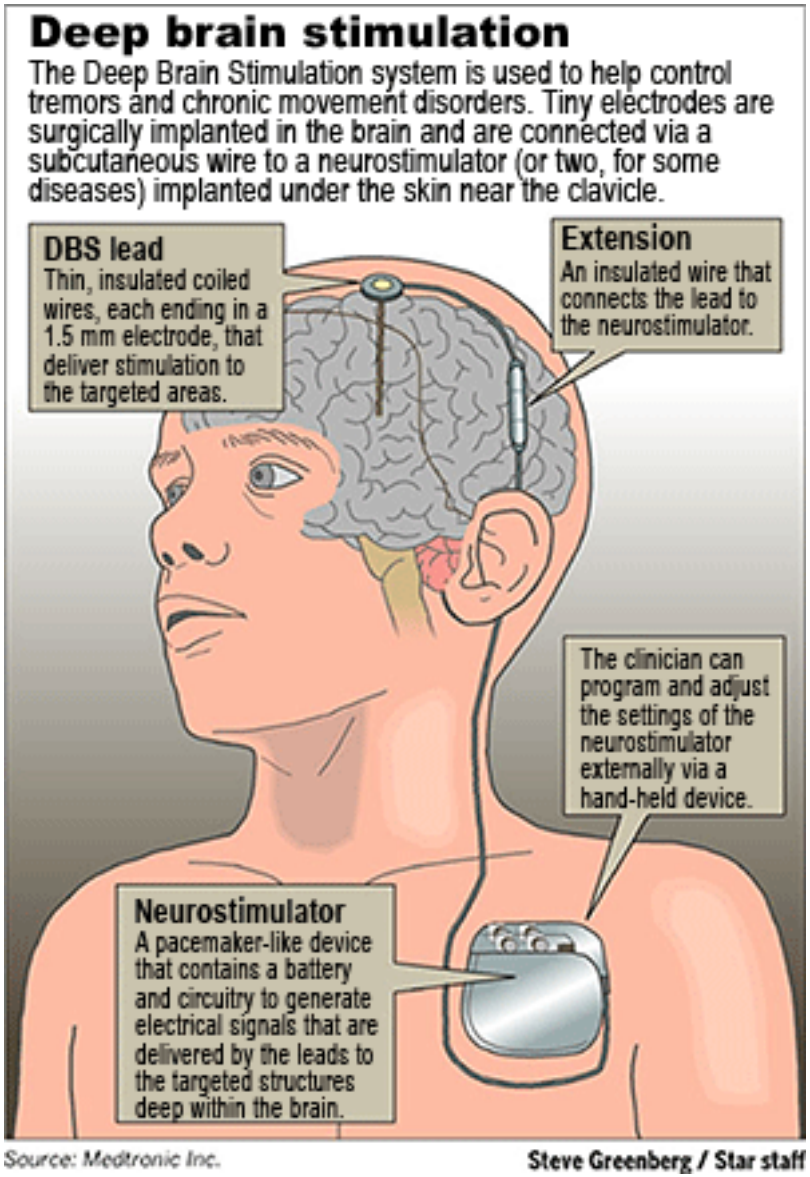




J Coste et al., 2009

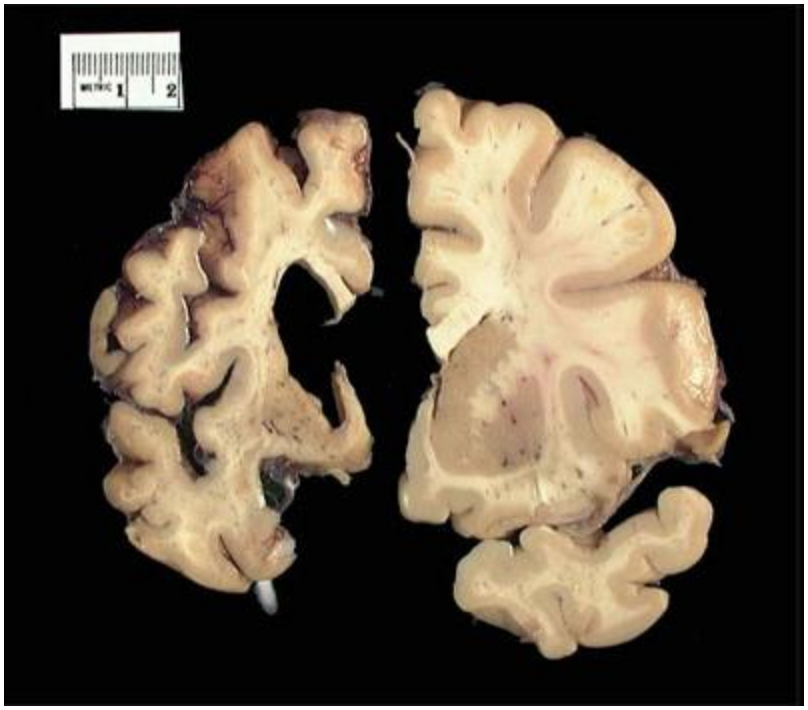
FIG. 1. (A) Example of stereotactic MRI anatomical mapping and primary targeting (*r*, right hemisphere, white bar = 1 cm): (top) anatomical mapping (label + outline) on a coronal T2-weighted slice (raw image), thalamus (thal), substantia nigra (sn), subthalamic nucleus (stn), zona incerta (zi), fields of Forel (ff), nucleus of the ansa lenticularis (nal) and red nucleus (rn), inlet, close-up on the interpolated image; (bottom) primary anatomical targeting, reconstructed and interpolated pseudo-coronal slice along the right central track (blue line), inlet, 3D view of the right trajectory. (B) Pattern types of neuronal activity (*x*-axis, 3-s window), 0 = background noise, 1 = isolated activity, 2A = irregular low activity, 2B = irregular moderate activity, 2C = irregular high activity, 3 = low burst activity, 4 = high burst activity, 5 = rhythmic activity and 6 = permanent tonic activity.

Deep Brain Stimulation



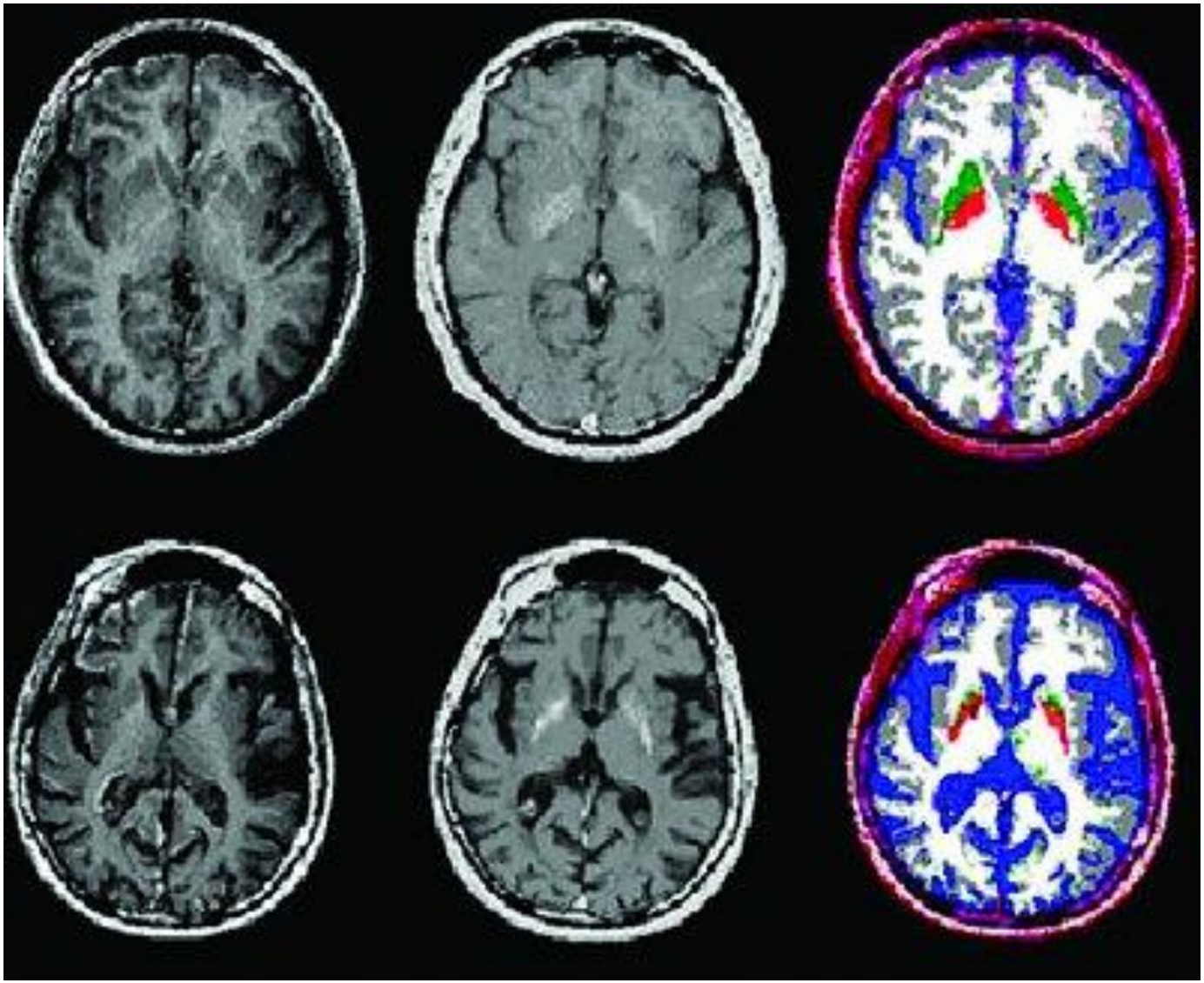
Huntington's disease

- **Huntington's disease (HD) is an autosomal dominant disorder caused by an expanded and unstable CAG trinucleotide repeat that causes a progressive degeneration of neurons, primarily in the putamen, caudate nucleus, and cerebral cortex**
- **HD is dominated by chorea and other involuntary movements during the clinical diagnosis of the disease**
- **However, it is becoming clearer that cognitive deficits appear before clinical diagnoses of motor abnormalities.**
- **These cognitive deficits include slowing of psychomotor speed, with impairment of attention and memory, as well as executive and visuospatial functions, that eventually degrade into dementia**
- **Currently, there is no effective treatment for the onset or progressive nature of the symptoms outside of small clinical trials using fetal grafts that slow the progression of the disease**



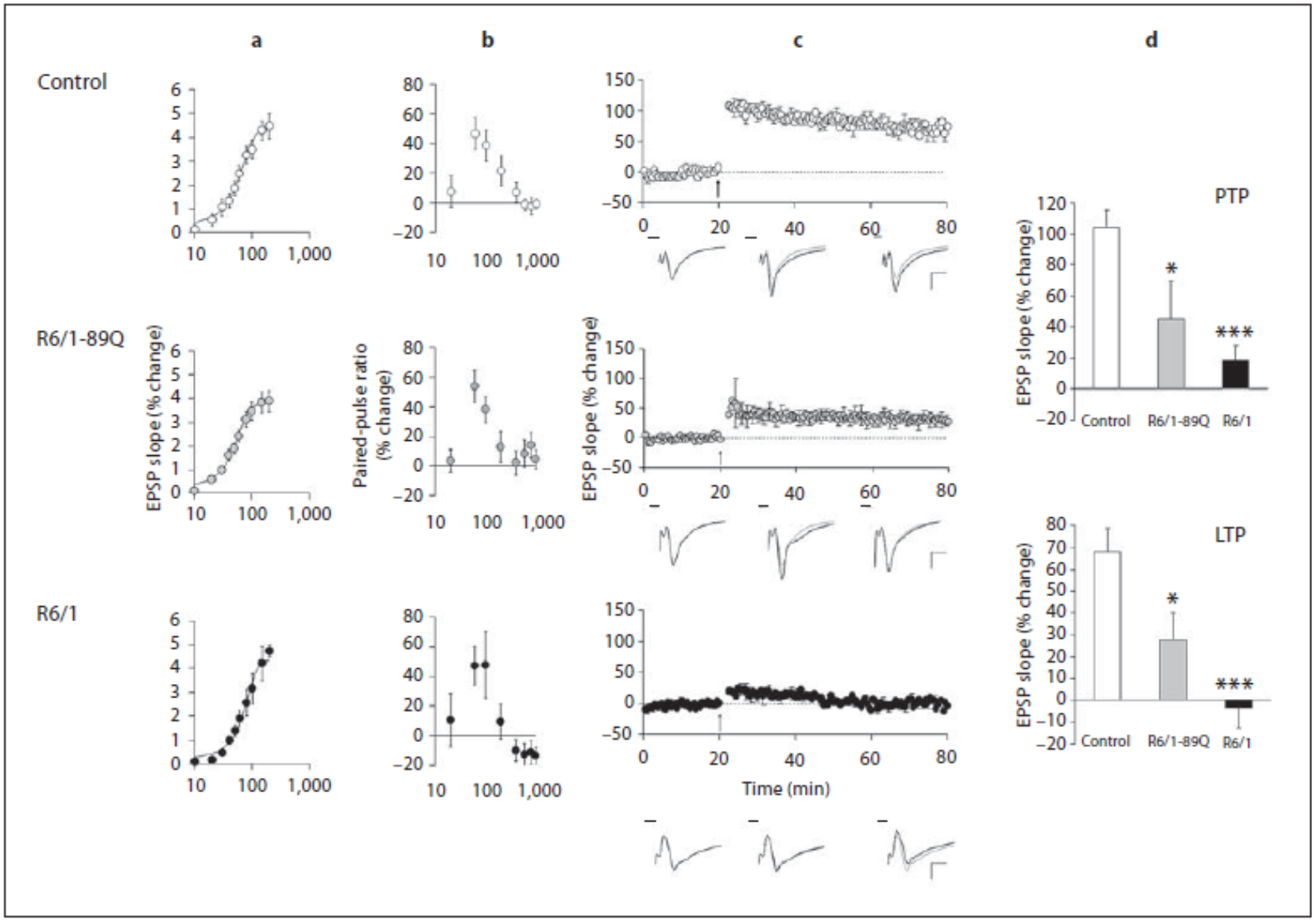
healthy subject

symptomatic Huntington's disease



Axial MR images. Note smaller fGM and fWM volumes in patient with Huntington's compared to healthy subject. Slices represent R1 and R2 relaxation rates and corresponding segmented images. Segmented images are coded gray for GM, white for WM, blue for CSF, green for putamen, and bright red for globus pallidus.

LTP and R6/1 mice model of Huntington's disease



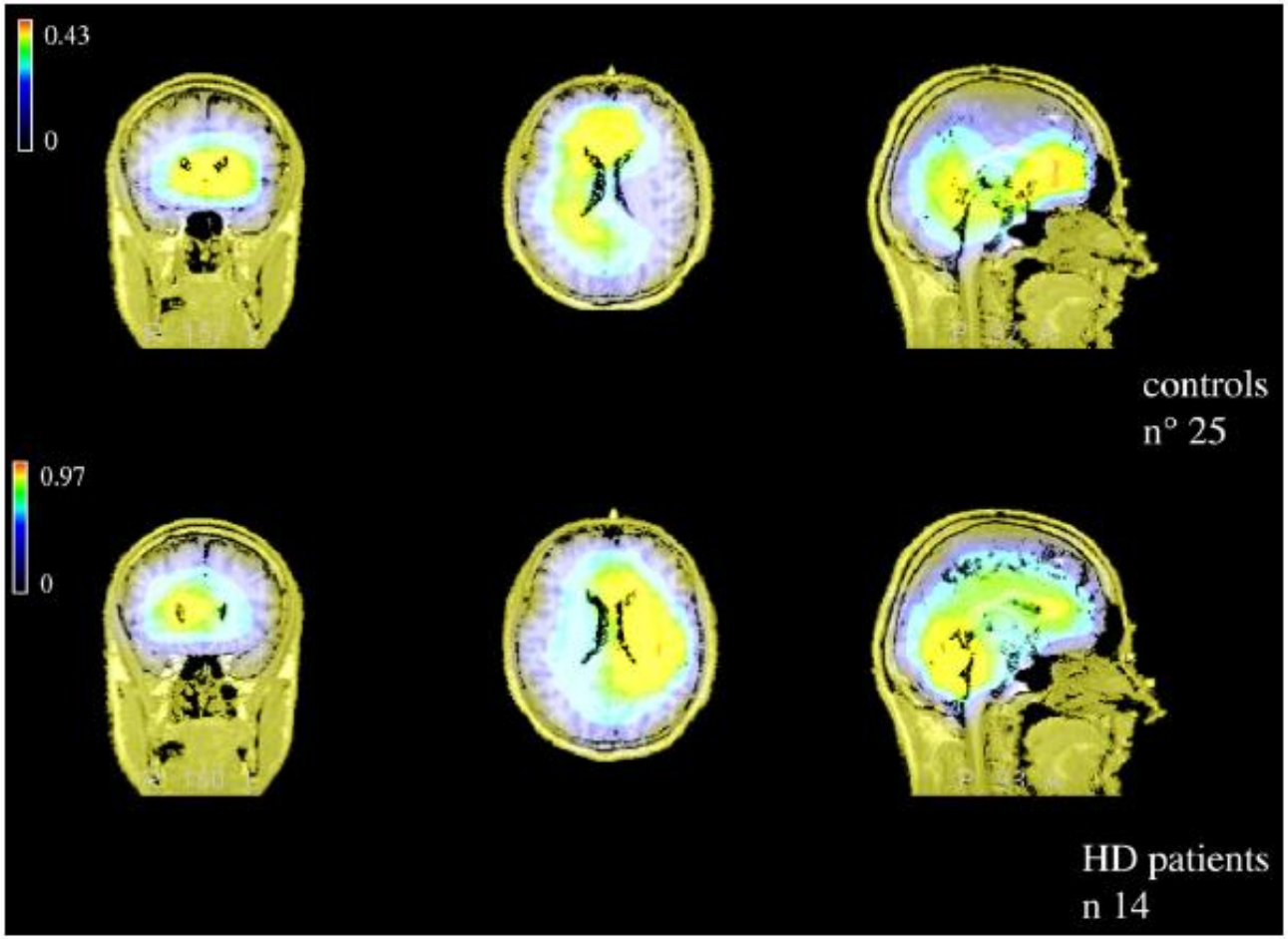


Fig. 2. LORETA analysis performed on the grand average of iCNV in patients and controls. The coloured maps express the strength of the 198 dipoles computed by ASA software on a realistically shaped boundary element model.

De Tommaso et al, 2007

Quantitative EEG in HD patients

- HD patients show a reduction in raw and percent alpha power, a decrease in raw and percent theta in the medial frontal area (Bylsma et al 1994).
- HD patients show suppressed alpha activity when compared to control patients (Bellotti et al, 2004; Bylsma et al 1994; de Tommaso et al, 2003; Streletz et al, 1990)
  - These abnormalities have been sourced to dysfunction of the thalamus (Bellotti et al, 2004 and de Tommaso et al, 2003)
  - MRI analysis has confirmed these reports with grey matter differences in the bilateral thalamus in symptomatic (Kassubek et al, 2005) and pre-HD (Wolf et al, 2009).

EEG in HD

- During a working memory task, pre-HD patients had significantly less alpha power when compared to control patients, despite performing normally in the memory task (van der Hiele et al, 2007)
  - Suggesting that while alpha power is decreased during a mental challenge, compensatory neuronal activity may keep performance intact.
- Alpha activity involves a complex thalamo-cortical network.
  - In HD fMRI blood-oxygen level dependent signal responses have shown dysfunction in prefrontal regions in both symptomatic (Thiruvady et al, 2007; Wolf et al, 2009) and pre-HD (Wolf et al, 2007 and 2008)

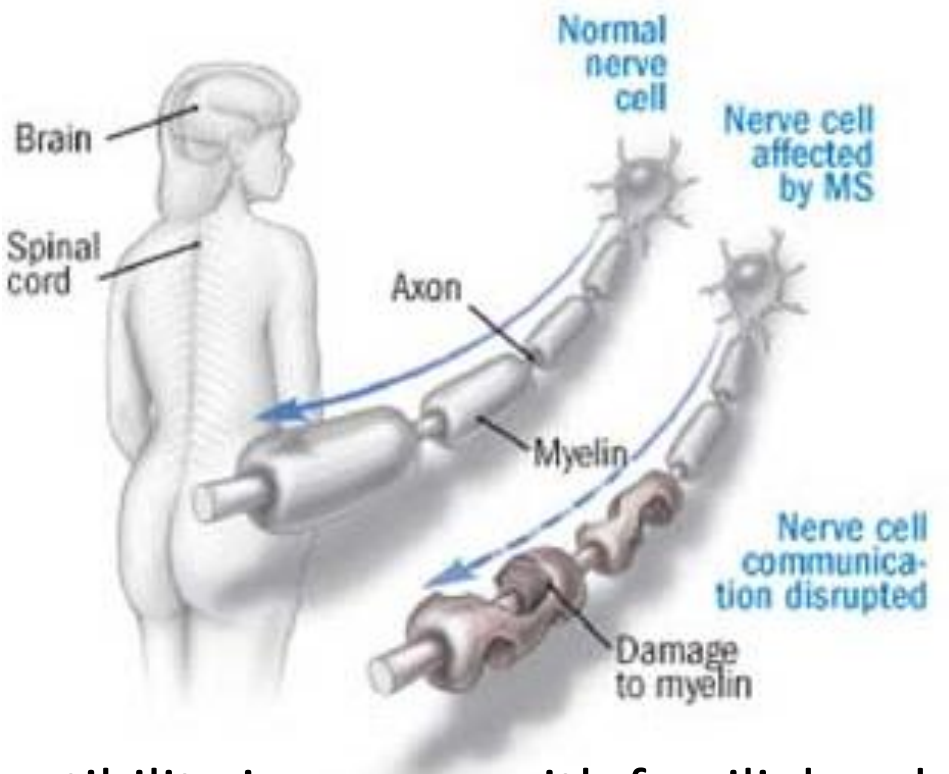
Sleep EEG in HD

- HD patients commonly report sleep disturbances such as insomnia, nocturnal waking, and daytime sleepiness.
  - HD patients have reduced sleep efficiency, prolonged sleep latency, reduced slow-wave sleep, and increased sleep spindles (Arnulf et al, 2008; Hansotia et al, 1985; Silvestri et al, 1995; Wiegand et al, 1991)
- HD sleep disturbances in the wake-sleep cycle have been partially attributed significant D2 receptor loss and microglia activation in the hypothalamus according to PET scans (Politis et al, 2008)

Multiple Sclerosis (MS)

- Patients' immune systems attack the central nervous system, increasing inflammation, and damaging myelin

- Demyelination and axonal block or axonal loss lead to evoked potential abnormalities such as delayed latency, morphological abnormalities, wave cancellation and increased refractory period.



- Cause is not known, though susceptibility increases with familial and geographical factors

Multiple Sclerosis - fMRI

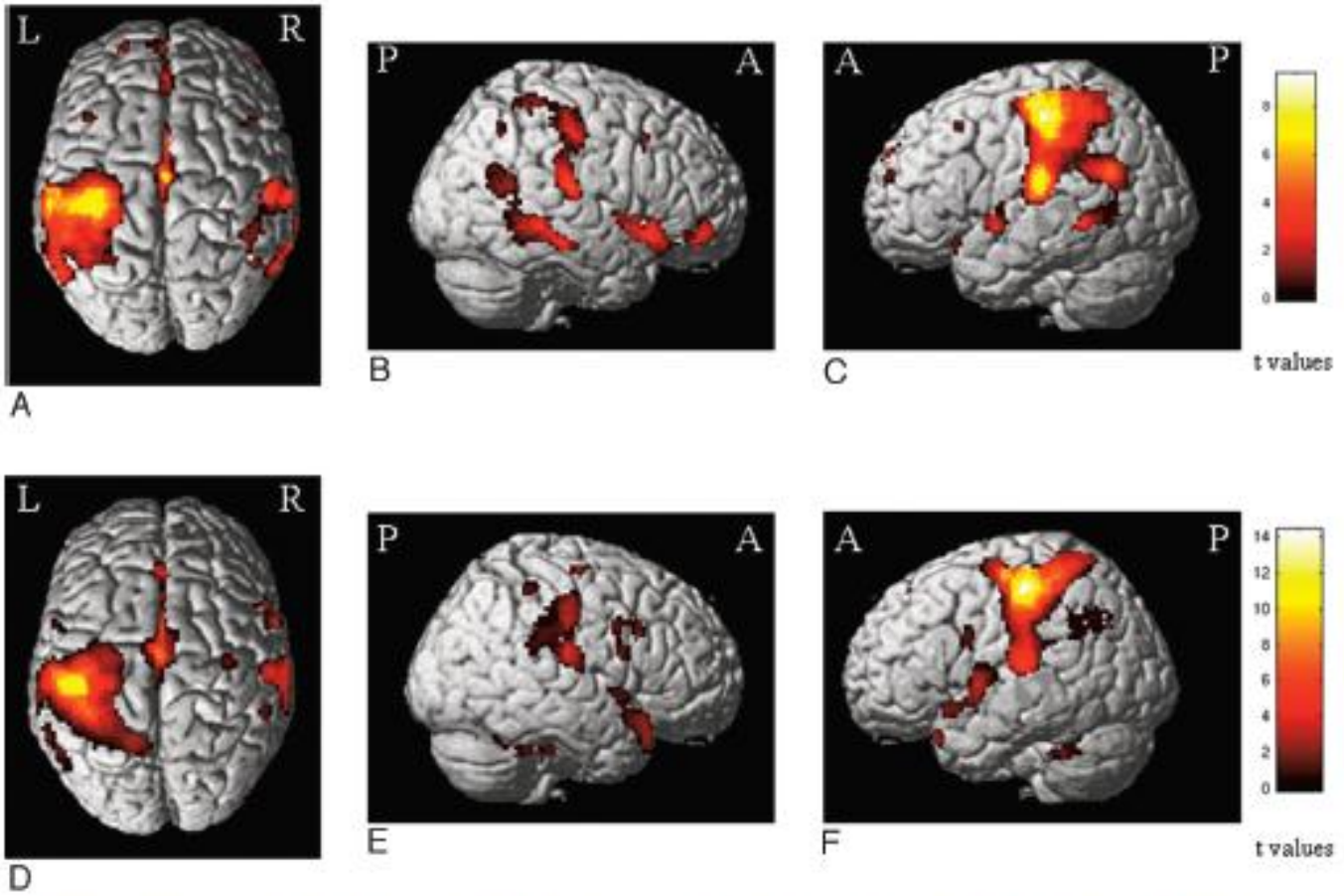


Fig 1. Areas showing BOLD changes in the within-group random-effects analysis (1-sample *t* test, $P < .001$, uncorrected for display purposes) during the 2-back task in healthy controls (*A–C*) and patients with PPMS (*D–F*). Note that the color-encoded activations have been superimposed on a rendered brain and normalized into the standard SPM space (neurologic convention).

Rocca, *et al.*, 2010

Multiple Sclerosis - Symptoms

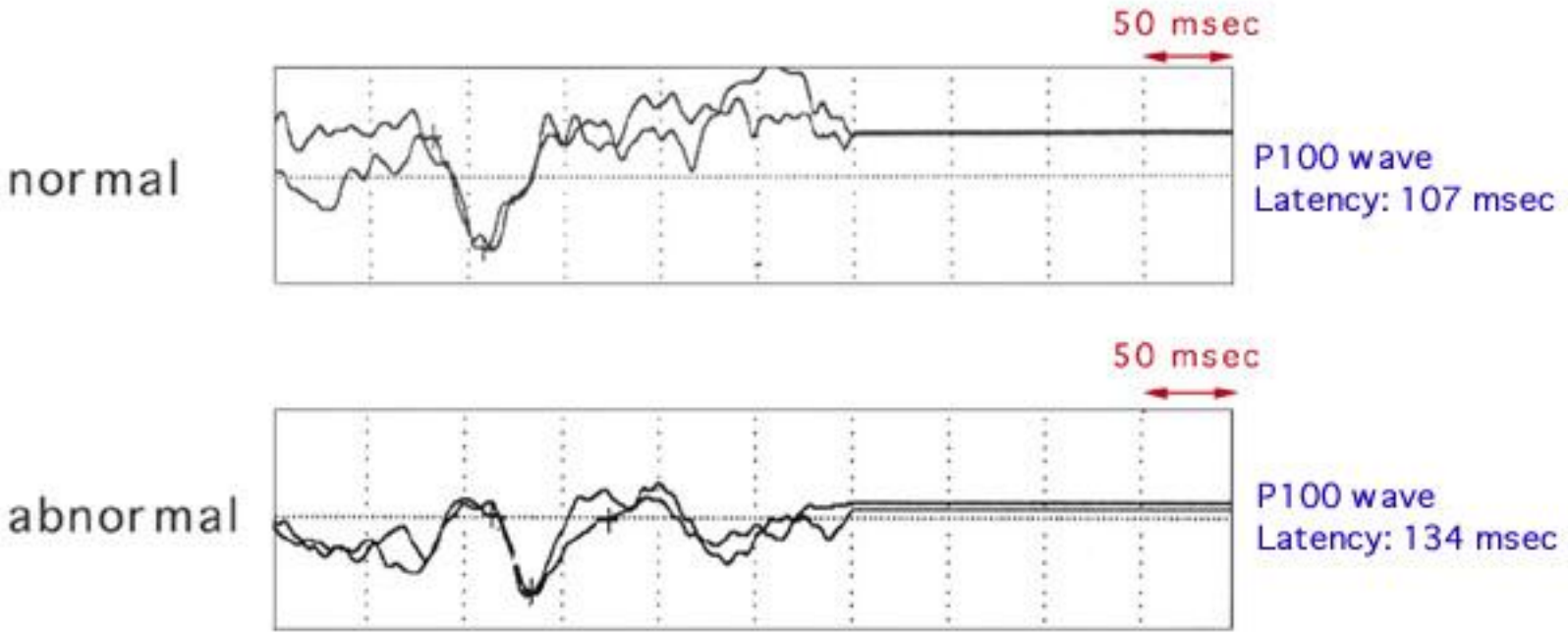
- Difficulty with movement
- Painful muscle spasms
- Numbness in the face and/or limbs
- Tremors and/or weakness of limbs
- Gradual vision loss
- Dizziness and loss of balance
- Cognitive decline

Multiple Sclerosis - Diagnostics

- Visual- and motor-evoked potential abnormalities
  - Frequency and severity of EP abnormalities correspond to duration of the disease and disabilities
  - Combined EPs are an emerging tool to predict long-tem disability
- fMRI is able to detect structural abnormalities
- Spinal tap measures levels of immunoglobulin proteins that may be increased in the cerebrospinal fluid of patients with MS

Multiple Sclerosis - Diagnostics

Visual Evoked Potentials



By John Rose, M.D.

Amyotrophic Lateral Sclerosis (ALS)

- Progressive motor neuron disease
- 3-5 year survival after initial symptoms
- Initial symptoms may be disregarded by patients for weeks or months
- ALS takes, on average, 1 year to diagnose following initial symptoms

ALS

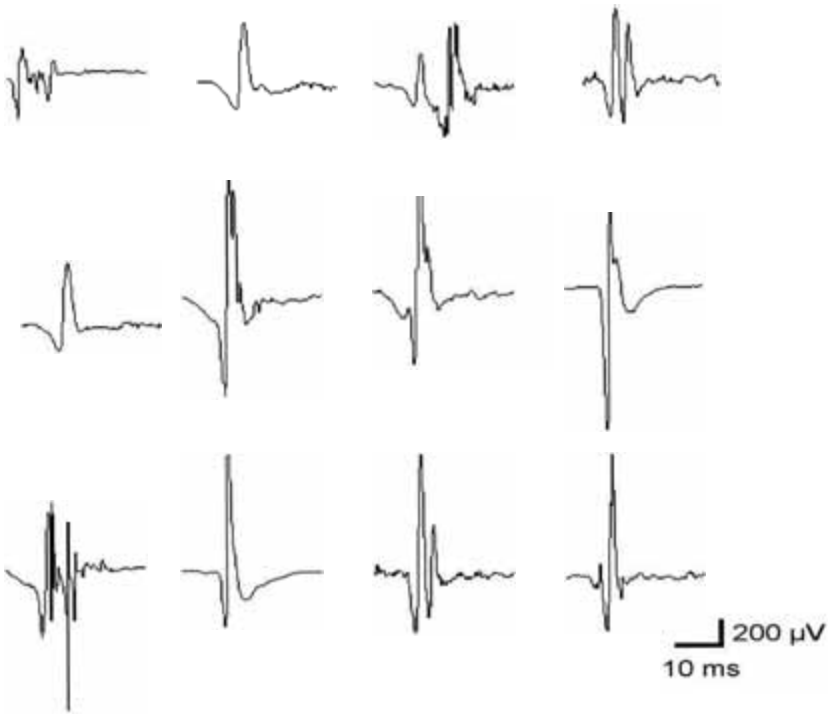
- Laboratory tests, MRI used to rule out other, more treatable diseases
- El Escorial Criteria(ECC(1998)), standard for ALS diagnosis
  - Based on clinical findings with EMG to support diagnosis
  - Criticized for rigidity, definitive diagnosis only in advanced ALS

ECC diagnosis of ALS

- Requires the presence of A- criteria and the absence of B- criteria
- A- Criteria
  - Degeneration of the lower motor neuron approved by clinical, electrophysiological, or neuropathological examination
  - Degeneration of the upper motor motor neuron approved by clincal examination
  - Progressive dissemination beyond typical nerve supply areas
- B- Criteria
  - Electrophysiological or neuropathological findings typical of other diseases which could explain the degeneration of upper and lower motor neurons
  - Findings in imaging studies which can explain clinical symptoms

Signs of chronic denervation in ALS

- Large motor unit potentials of increased duration with an increased proportion of polyphasic potentials, often increasing in amplitude



Motor Unit Action Potentials obtained from the biceps muscle of a patient with early ALS at slight innervation. Amplitudes are frequently higher than 1 mV and the configuration is frequently polyphasic.

From Dengler, 2010

ALS

- Reduced interference patterns with firing rates >10 Hz is a sign of chronic denervation
- A significant UMN component of ALS may cause firing rates <10 Hz and unstable motor unit potentials

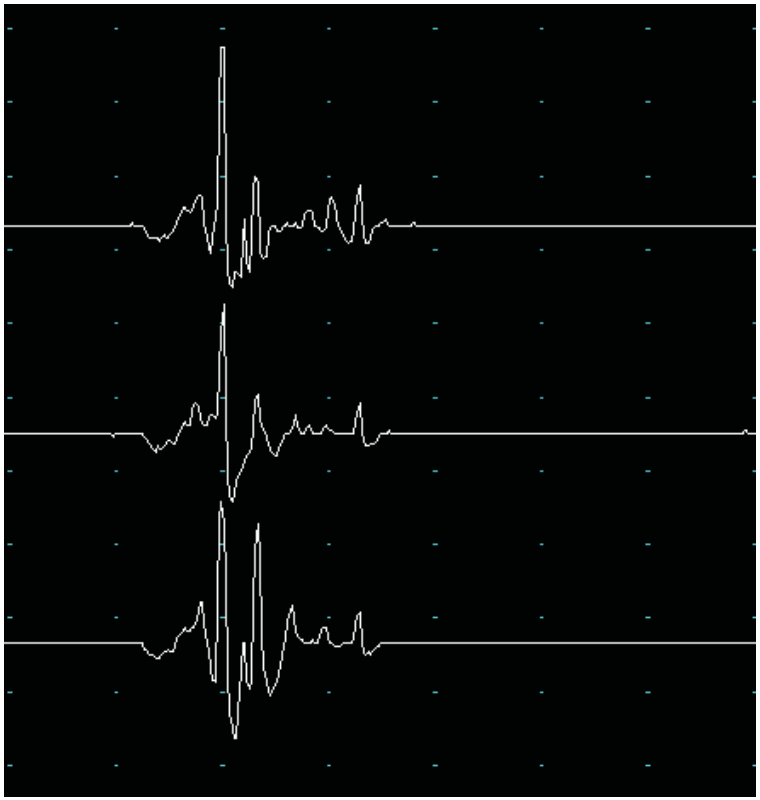


FIGURE 2. Unstable MUAP in the tibialis anterior muscle of a patient with ALS. The *configuration of the potential changes from discharge to discharge. Concentric needle electrode; filter setting 1 kHz to 10 kHz; calibration: 5 ms / Div. and 100 uV / Div.*

Nerve conduction studies in ALS

- Required for diagnosis of ALS
  - Used to exclude motor neuropathy or other disorders of peripheral nerve, neuromuscular junction, and muscle that may mimic ALS
  - Sensory nerve conduction studies should be normal in ALS
  - May be augmented in patients with co-existing entrapment syndromes or peripheral nerve disease

Upper motor neuron signs in ALS

- Transcranial magnetic stimulation (TMS) may help to identify upper motor neuron signs
  - Changes in central motor conduction times to arm or leg muscles
  - Side to side differences in size of motor evoked potentials (MEP)
  - Specificity and sensitivity questionable, may not be relevant to diagnosis of ALS

ALS

Table 2. Signs and symptoms of UMN and LMN degeneration.

UMN signs and symptoms

- Pseudo bulbar features
  - Exaggerated affect
  - Forced yawning
  - Exaggerated snout reflex
- Spastic tone
- Pathologic tendon reflexes
  - Clonic jaw reflexes
  - Pathologic spread
  - Clonus
  - Preserved reflex in weak, wasted limb
- Pathologic responses
  - Exaggerated gag reflex
  - Hoffmann response
  - Extensor plantar response (Babinski's sign)

LMN signs and symptoms

- Atrophy
- Fasciculation's
- Weakness

From Oliveira & Pereira, 2009

ALS

Table 3. World Federation of Neurology Electrodiagnostic Proposed Criteria for LMN Degeneration.

Signs of active denervation

- Fibrillations
- Positive waves

Signs of chronic partial denervation

- Motor unit potential with increased duration
- Frequent polyphasia with instability
- High amplitude
- Reduced recruitment except in the presence of significant UMN dysfunction

From Oliveira & Pereira, 2009

Diagnostic Criteria for ALS

Table 4. World Federation of Neurology (El Escorial) criteria for diagnosis of ALS.

The diagnosis of ALS requires

1) The presence of
   - Evidence of LMN degeneration on clinical, electrophysiologic (including EMG features in clinically normal muscles) or neuropathologic examination
   - Evidence of UMN degeneration on clinical examination
   - Progression of the motor syndrome within a region or to other regions, as determined by history or examination; and
2) The absence of
   - Electrophysiological and pathological evidence of other process that might explain the UMN and / or LMN signs; and
   - Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs

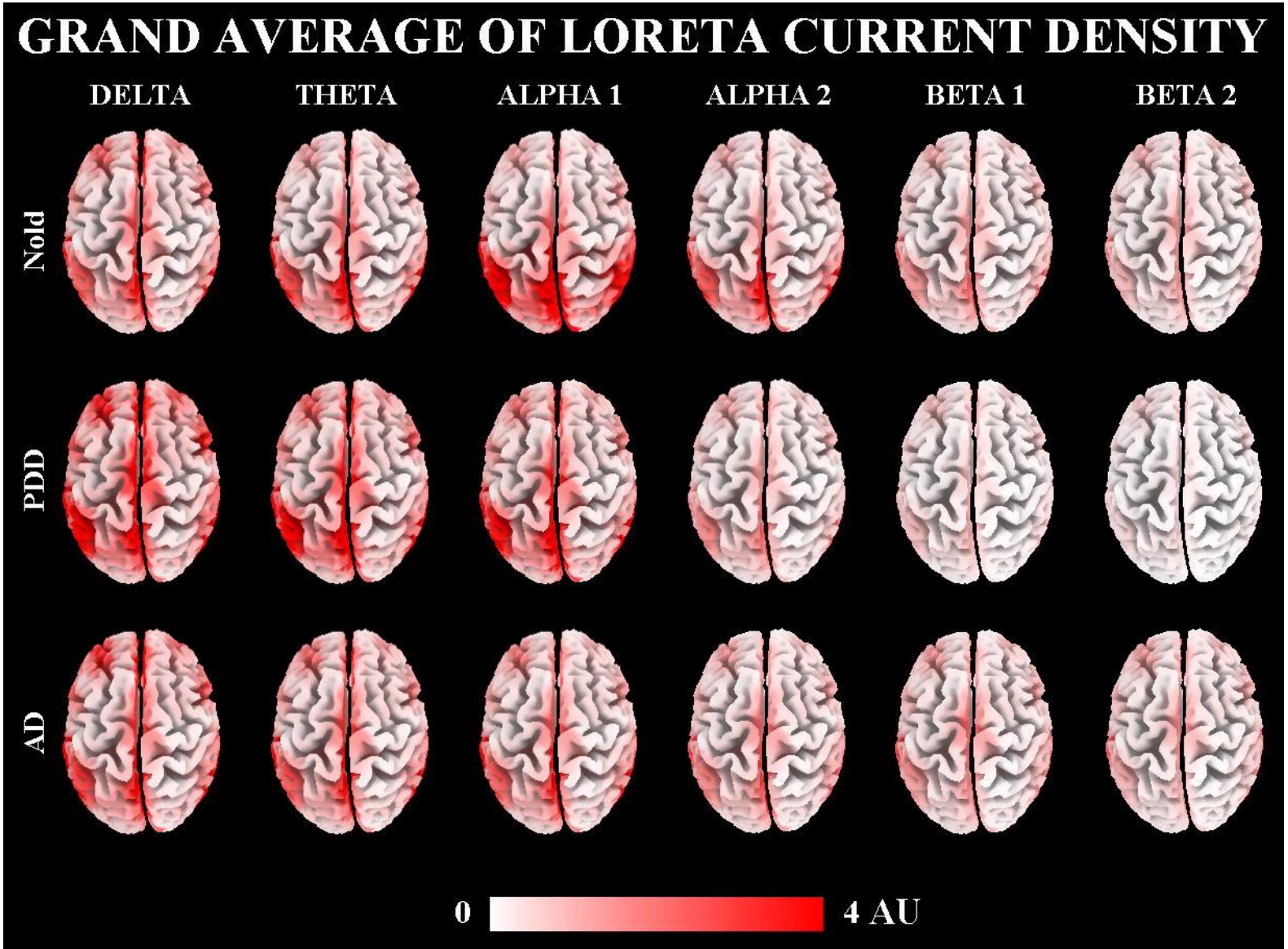
From Oliveira & Pereira, 2009

Putting it all together

- There are numerous electrodiagnostic correlations with various aspects of neurodegenerative diseases
- New developments in technology and methods of analyses are yielding new insights into both normal brain function and dysfunction
- Although current diagnostic abilities are relatively limited in their ability to provide reliable diagnostic distinctions of the various neurodegenerative processes, future developments in this quest look promising.

Low Resolution Electromagnetic Tomography

Differentiate between AD and PD patients. Results of EEG correlated with Mini Mental State Examination (Babiloni C et al 2011).



Summary

1. Electroneurodiagnostic tools are useful in diagnosing and monitoring the course and treatments of neurodegenerative diseases.
2. Increased use of these tools will help in better elucidating the underlying mechanisms of the neurodegenerative diseases.
3. Expanded use of electrophysiology for treating neurodegenerative diseases (e.g., BBS) and developments of new strategies (stimulation of stem cell implants) will provide more effective means for treating neurodegenerative diseases in the future.

Post-Test

1. A critical receptor type for mediating LTP is the:

   a. D2 b. NMDA c. GluR2 d. D4

2. Increases in which band frequency is most commonly associated with severe Alzheimer's:

   a. 2-5 Hz b. 7-11 Hz c. 14-18 Hz d. 20-24 Hz

3. A common DBS target for PD patients is the:

   a. CN b. SNc c. SNr d. STN

4. Which of the following is suppressed in HD:

   a. alpha b. beta c. theta d. delta

5. A delay in VEP is seen often in patients with:

   a. AD b. PD c. HD d. MS

Questions?

Diagnostic Criteria for ALS

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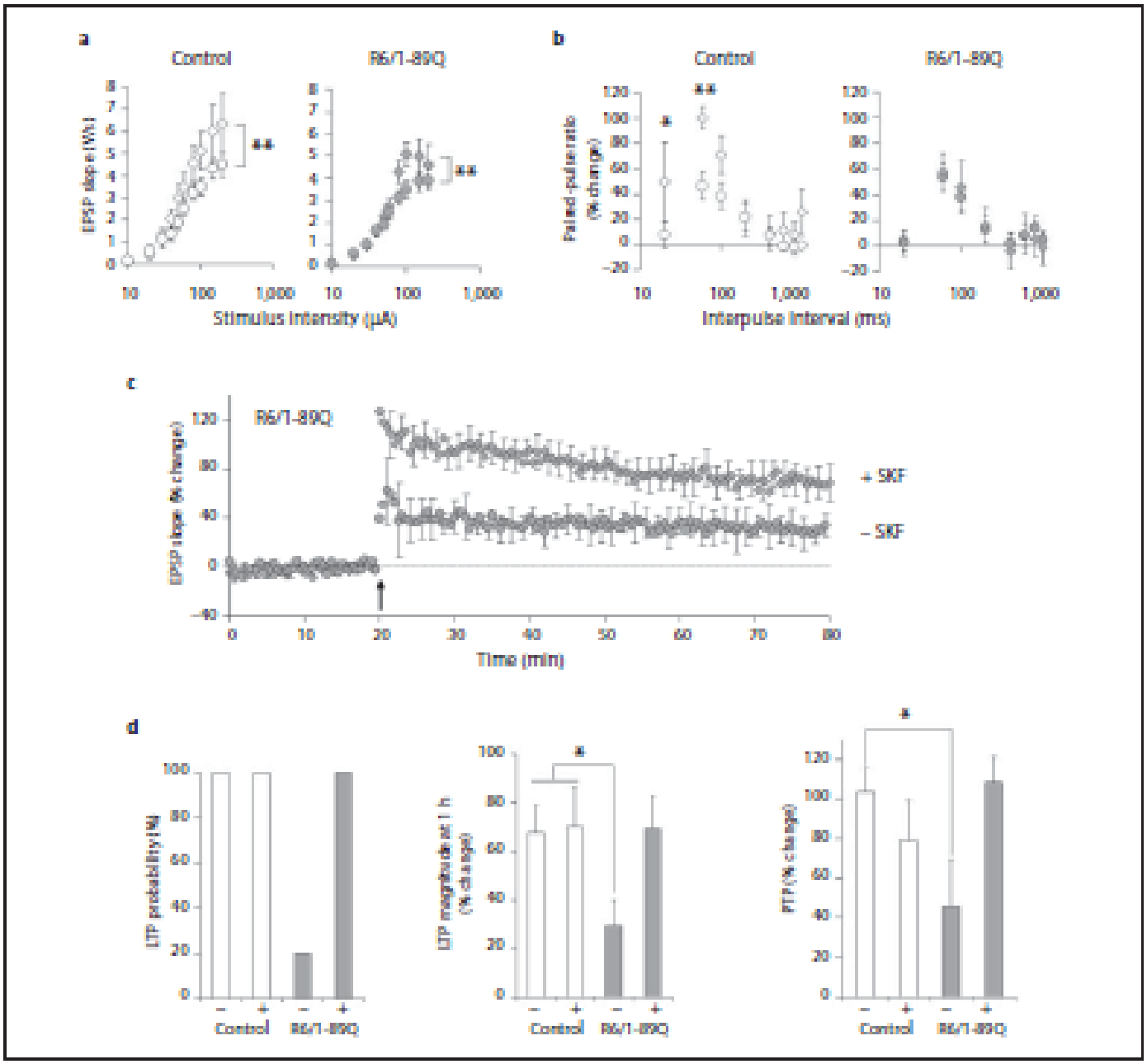
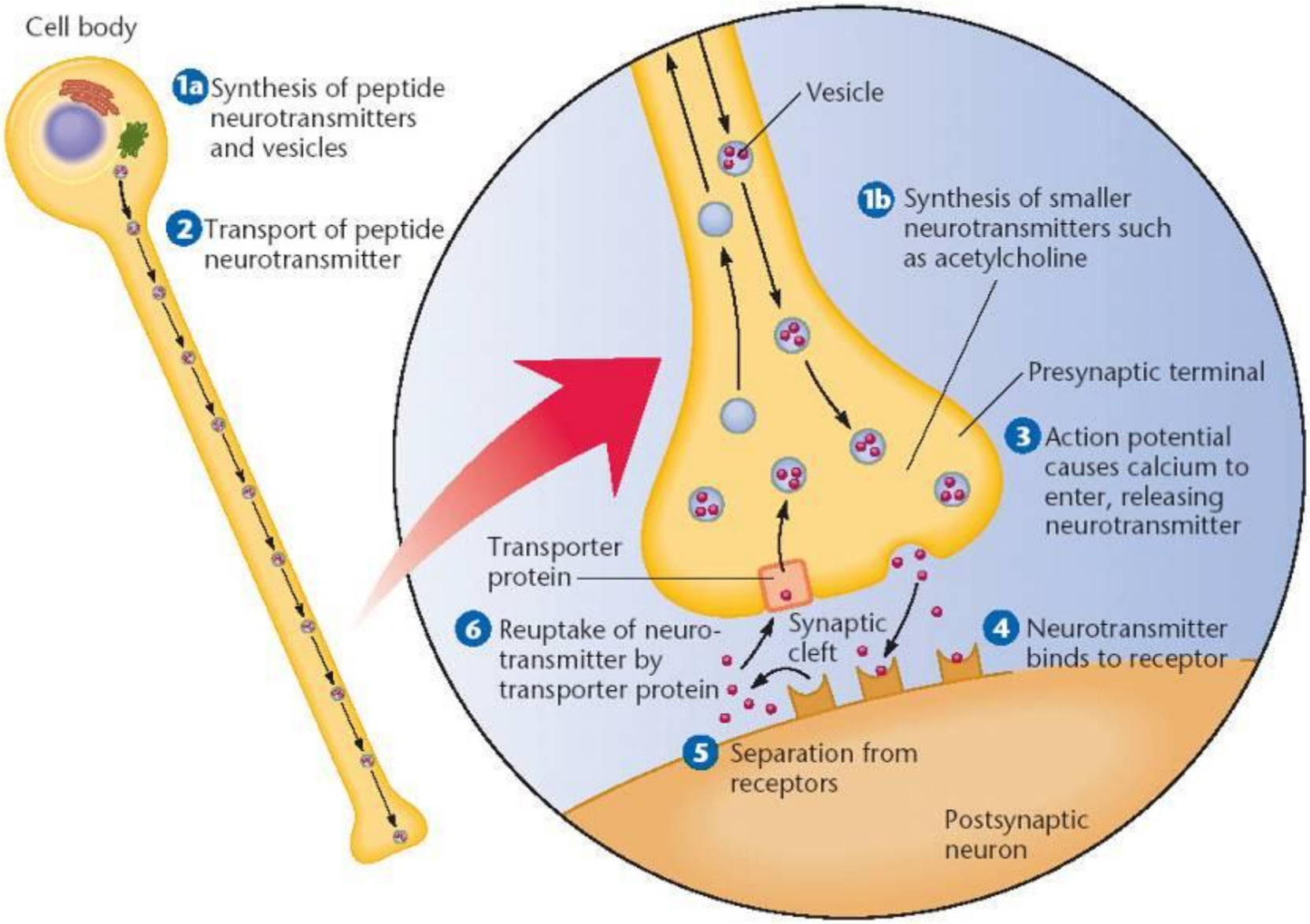
Diagnostic Criteria for ALS

LTP and R6/1 mice model of Huntington's disease



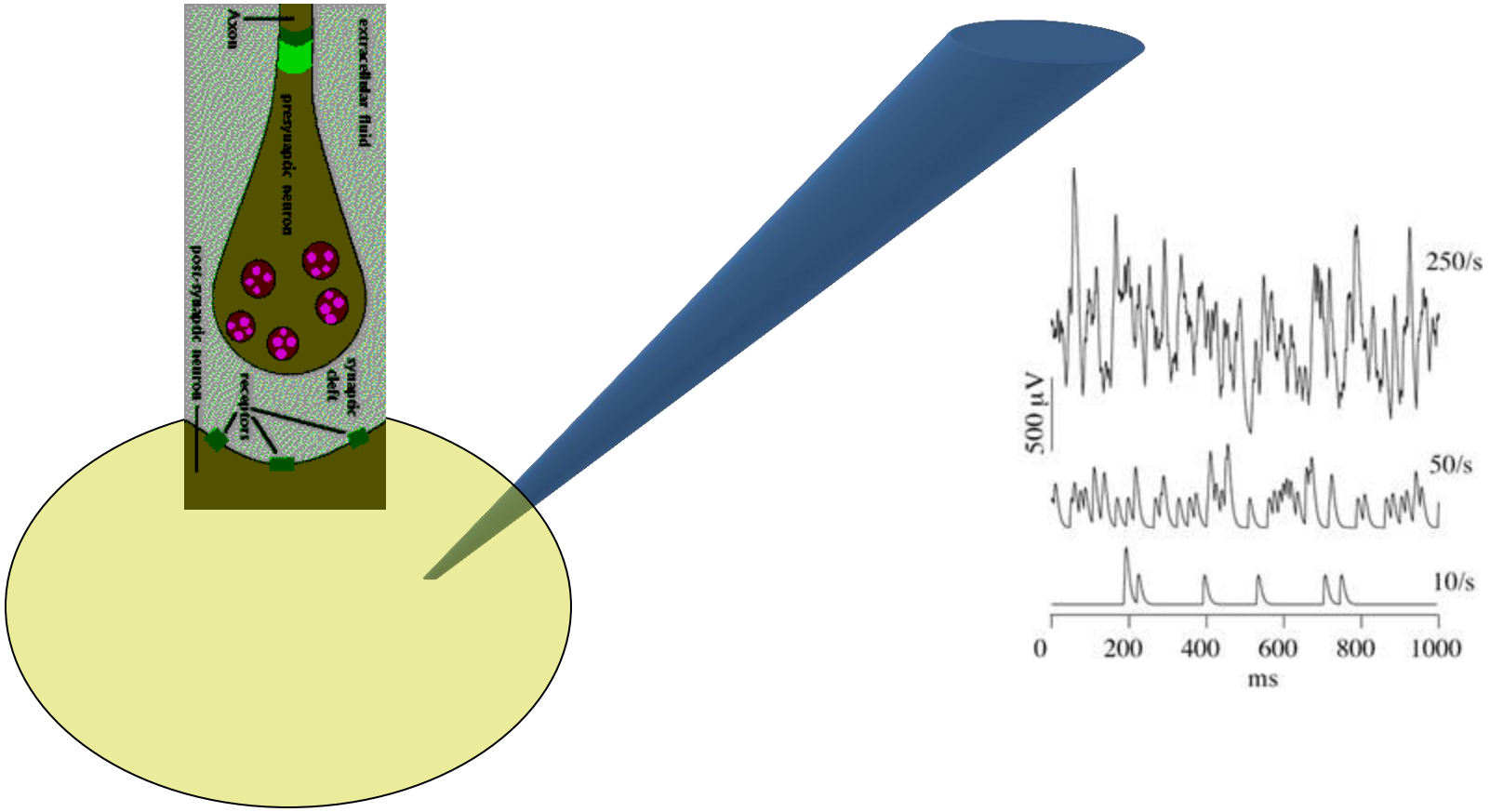
Diagnostic Criteria for ALS

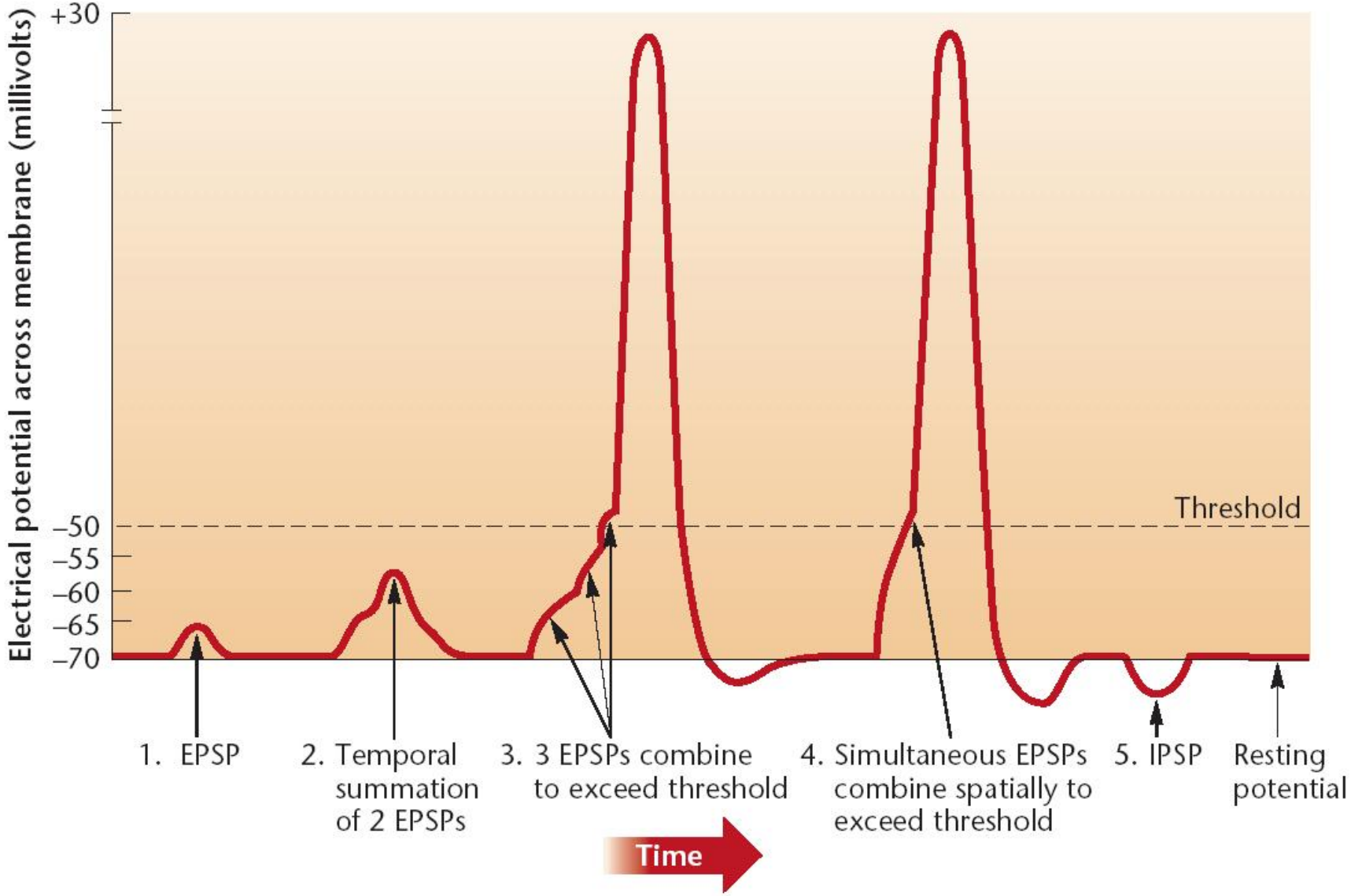

Cell body
1a Synthesis of peptide neurotransmitters and vesicles
2 Transport of peptide neurotransmitter
Vesicle
1b Synthesis of smaller neurotransmitters such as acetylcholine
Presynaptic terminal
3 Action potential causes calcium to enter, releasing neurotransmitter
Transporter protein
6 Reuptake of neuro-transmitter by transporter protein
Synaptic cleft
4 Neurotransmitter binds to receptor
5 Separation from receptors
Postsynaptic neuron

Postsynaptic Potentials

- **EPSP**: Excitatory Post Synaptic potential
  - Neurotransmitter causes local, graded depolarization on the postsynaptic neuron
- **IPSP**: Inhibitory Post Synaptic Potential
  - Neurotransmitter causes local, graded hyperpolarization on the postsynaptic neuron
- **Quanta**: the amount of neurotransmitter stored in a single synaptic vesicle, thus the lowest level potential postsynaptic effect

Intracellular Recording can measure Quanta




Electrical potential across membrane (millivolts)
+30
–50
–55
–60
–65
–70
Threshold
1. EPSP
2. Temporal summation of 2 EPSPs
3. 3 EPSPs combine to exceed threshold
4. Simultaneous EPSPs combine spatially to exceed threshold
5. IPSP
Resting potential
Time

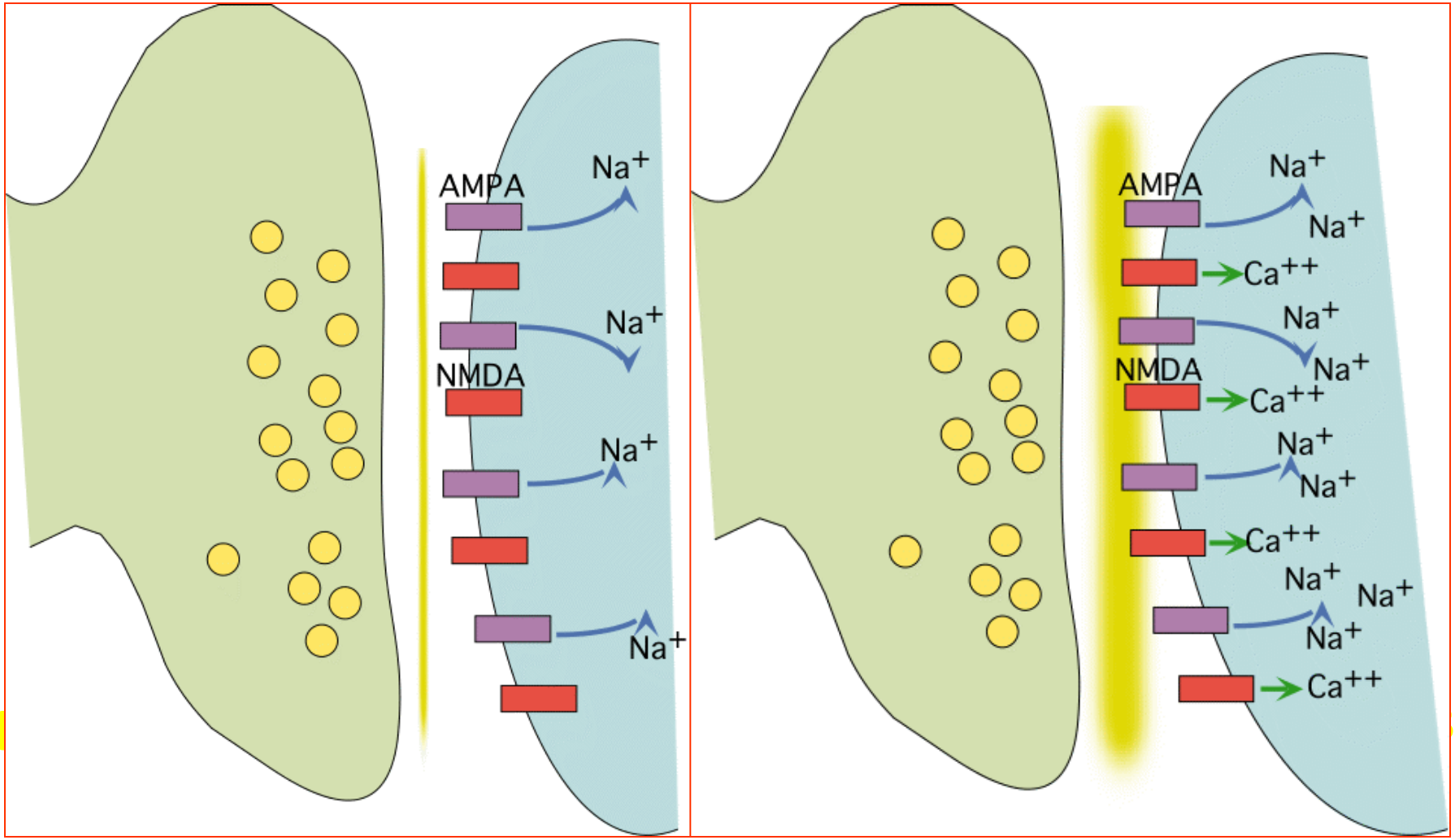
Ways cell A could stimulate cell B more effectively

1. Cell A could release more neurotransmitter
   - Cell A could increase synaptic vesicles released or transmitter contained in vesicles
   - Cell A could increase number of axon terminals that synapse with cell B
2. Cell B could become more sensitive
   - Cell B could decrease dendritic spine length
   - Cell B could increase number of receptors
   - Cell B could increase sensitivity of receptors

Mechanism of LTP

- Glutamate activates AMPA receptors and depolarizes membrane causing release of magnesium from NMDA receptor.
- Sodium and calcium rush in NMDA receptor and calcium activates CaMKII, which increases dendritic branching.
- Retrograde transmitters causes increase production of GAP-43 in presynaptic cell, leading to axonal growth

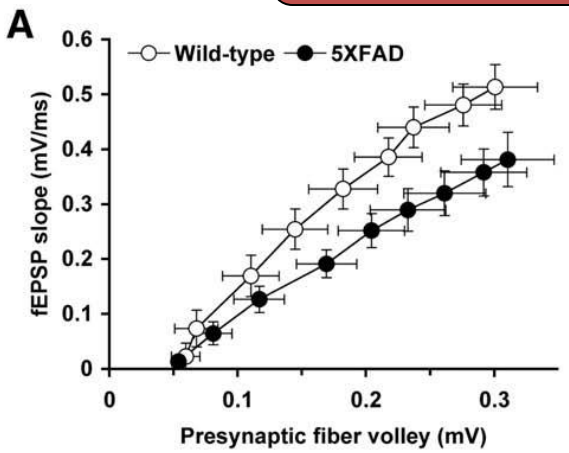
LTP and the NMDA Receptor

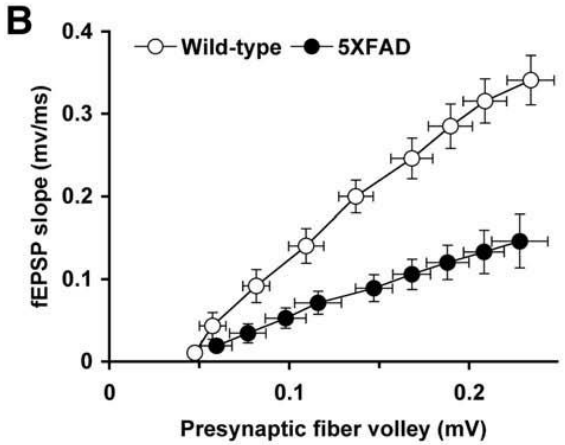


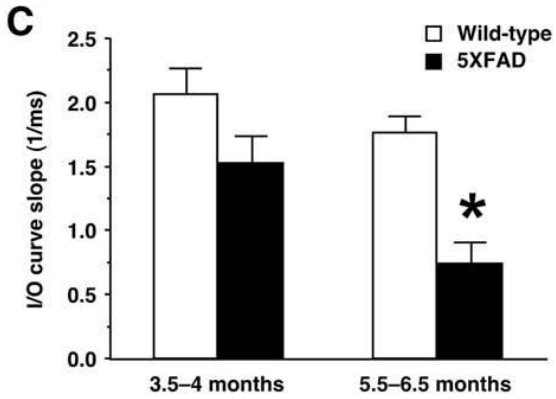
After Ca^{2+}, CAMKII

- Calcium calmodulin kinase II linked to…
  - Phosphorylation of AMPA receptors, increasing their sensitivity
  - Increased numbers and strategic placement of AMPA receptors
  - “Silent” (unresponsive) AMPA receptors becoming active
  - Branching of dendrites (additional synapses with same axon)

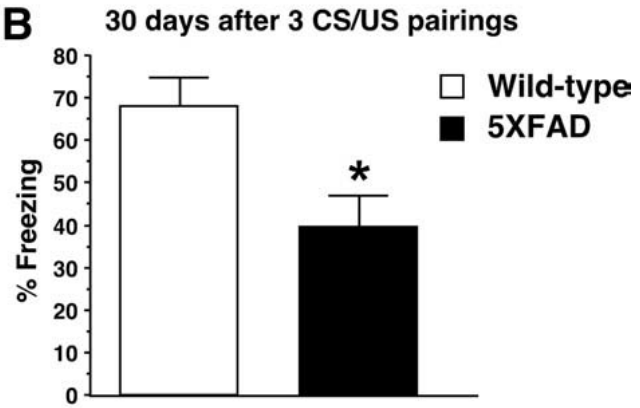
Rodent Studies with Electrophysiology







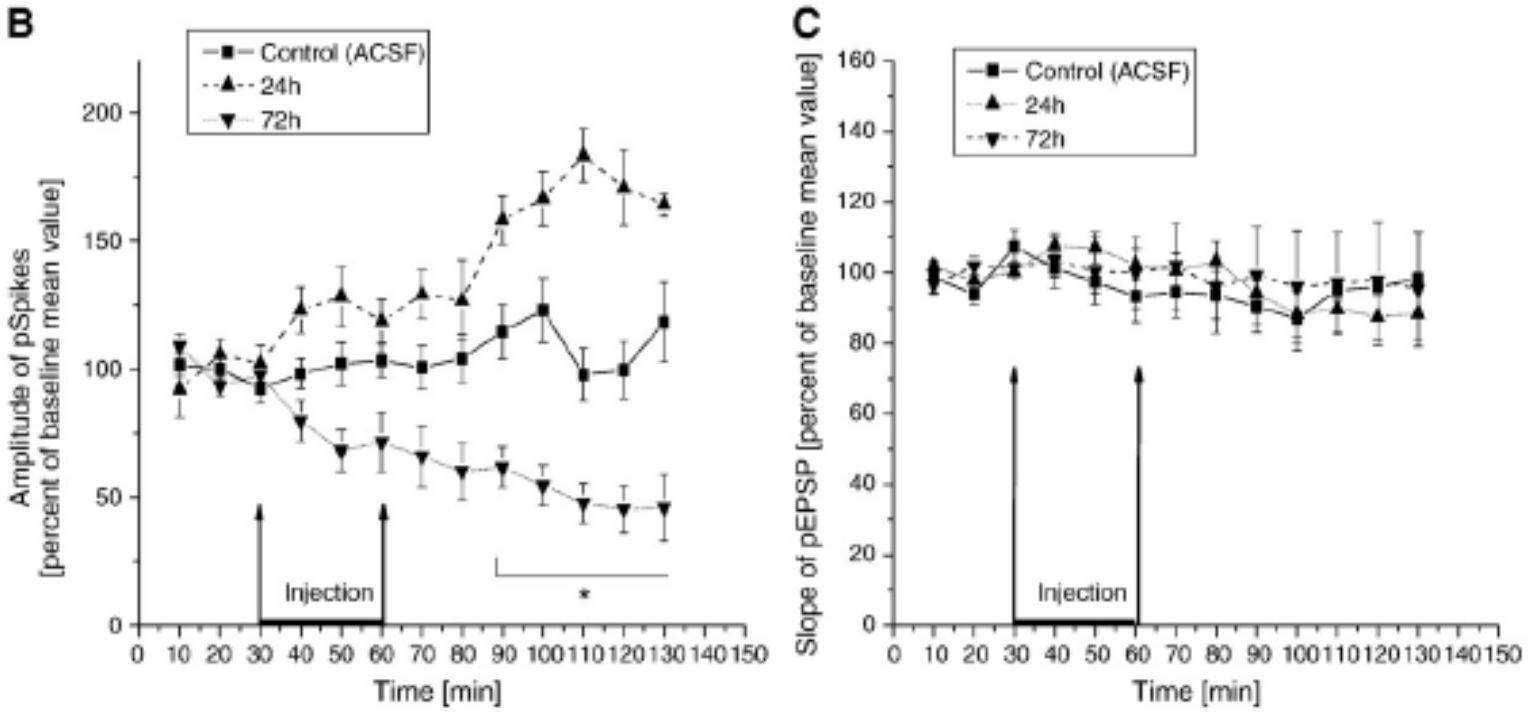
- Kimura & Ohno, 2009: **hippocampal slices**



- Same age deficits in classical conditioning

Effects of Aβ

- Injection of Aβ that has been cultured for 72 hrs decreases in amplitude in freely moving rats (Orbán et al, 2010)



Diagnosis

- Results of PET/MRI reveal these differences in thickness and activity (Karrow et al 2010)