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# Anti-NMDA receptor Encephalitis

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# Background

- Auto-immune disorder
- 81% of cases affect women
- Median age of diagnosis is 21 years
- Associated with ovarian teratomas
- 75 % diagnosed recover, mortality rate is 7 % (according to a 2008 study)
- Categorized and named by Joseph Dalmau, 2007
- Symptoms mimic described characteristics of demonic possession
- Commonly undiagnosed or misdiagnosed, e.g. as bipolar disorder



# Symptoms

## Prodromal

- Headaches
- Flu-like symptoms
- Fatigue
- Fever

*“When he suggested I try to relax, I turned to face him, staring past him like I was possessed. My arms suddenly whipped straight out in front of me, like a mummy, as my eyes rolled back and my body stiffened. I was gasping for air... Blood and foam began to spurt out of my mouth through clenched teeth... I would never regain any memories of this seizure, or the ones to come.” - Susannah Cahalan, *Brain on Fire**

## Progression

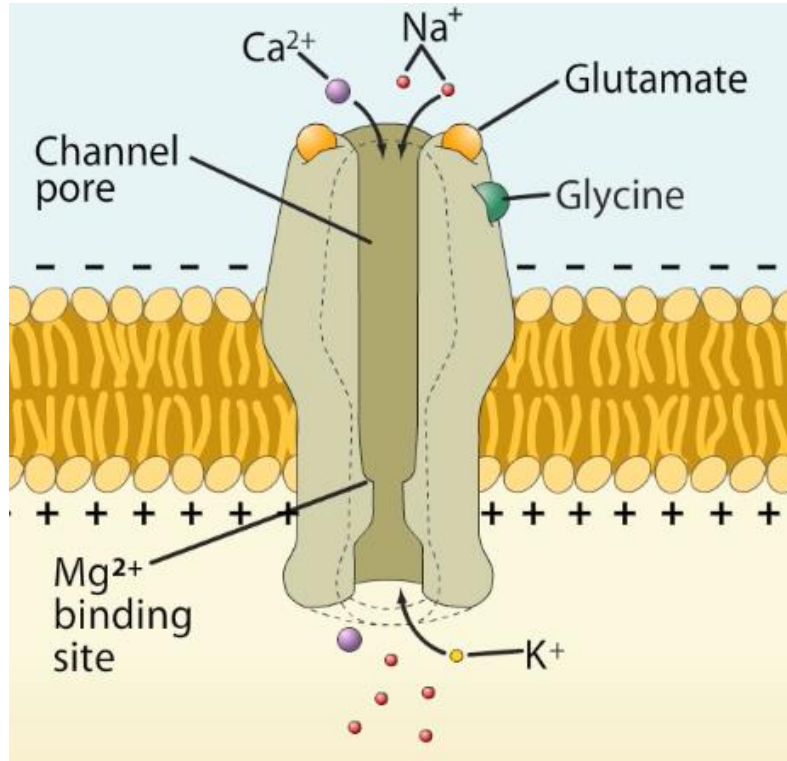
- Paranoia
- **Psychosis**
- **Seizure**
- Cerebellar ataxia
- **Memory deficits**
- Speech problems (aphasia, perseveration, mutism)
- **Motor symptoms**
- Hemiparesis
- Hypoventilation
- Delusions and/or hallucination
- Catatonia

# Diagnosis

- Psychological, cognitive tests
- Anti-NMDAR antibody cerebral spinal fluid (CSF) analysis
- MRI scan for lesions (cortex, basal ganglia, thalamus)
- Brain biopsy



# NMDA receptor



## Specific functionality

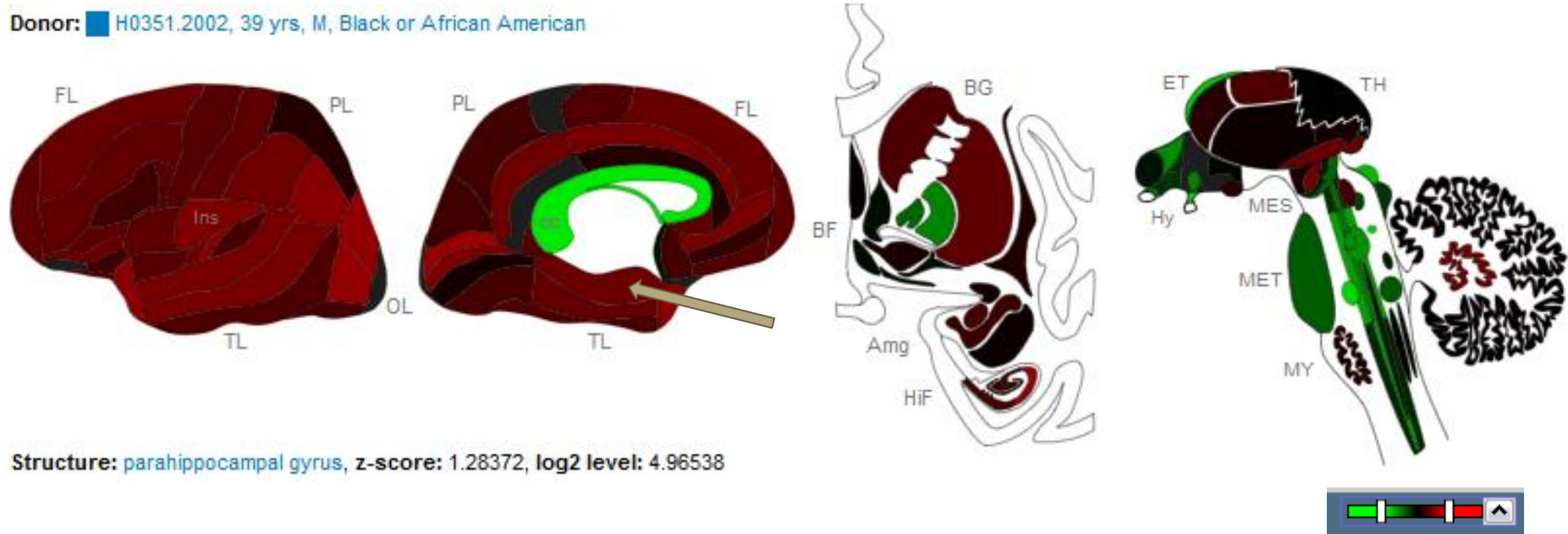
- Glutamatergic
- Ionotropic
- $\text{Na}^{+}$  and  $\text{Ca}^{++}$  permeable
- Excitatory response
- Magnesium plug is removed when the membrane is depolarized
- Glycine is a co-agonist
- Heterotetramer (two NR1 subunits, two NR2 subunits)

## Brain functionality

- Synaptic plasticity
- Calcium can function as a second messenger after an action potential
- Memory formation, learning, synaptogenesis

# NMDA receptor localization

Donor: H0351.2002, 39 yrs, M, Black or African American

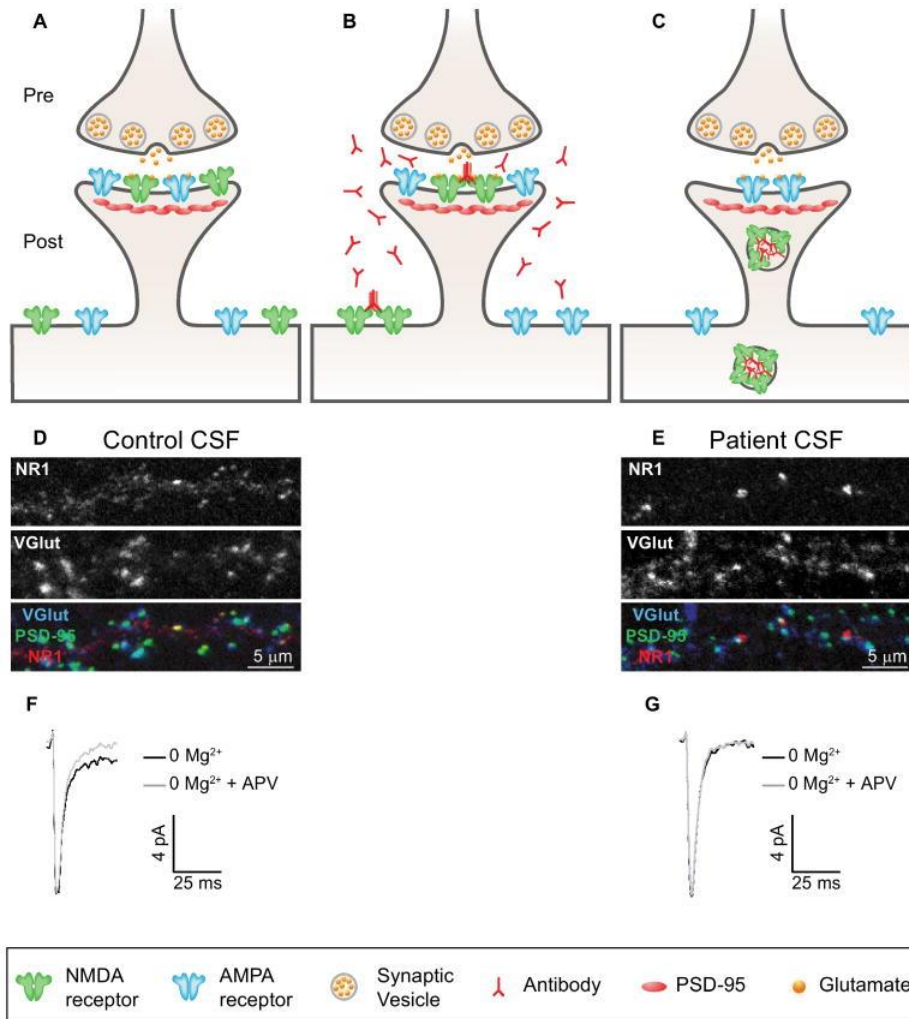


Structure: parahippocampal gyrus, z-score: 1.28372, log2 level: 4.96538

# Proposed Mechanisms of Action

1. BBB damage
  - a. Acute inflammation
  - b. CRH and mast cell interaction
  - c. Autonomic dysfunction (i.e. increased blood pressure)
2. Intrathecal antibody production
3. Excessive levels of antibodies in the CSF induce degradation of NMDAR GluN1 subunit
  - a. NMDAR cross-linkage
  - b. Direct antagonism of NMDAR
  - c. Complement cascade

# NMDAR cross-linkage



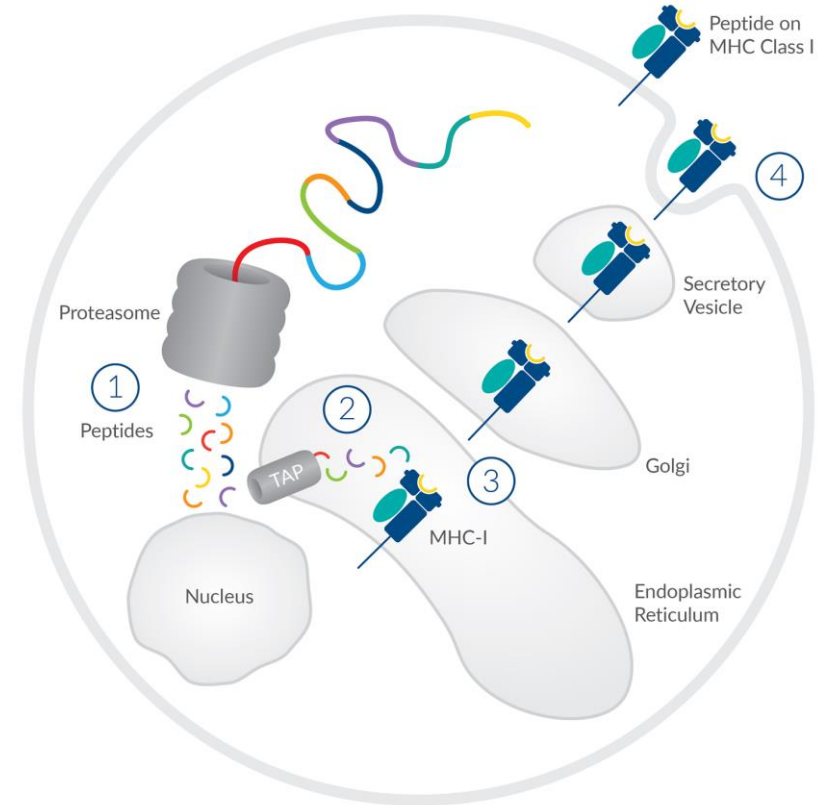
- Localization of AMPA and NMDA receptors at PSD
- Selective binding of antibodies to NMDAR and receptor cross-linking
- Internalization of antibody-bound NMDAR
- Cultured rodent neurons treated with control CSF and stained for NR1, VGlut, and PSD-95
- Patient CSF treatment
- CSF control of mEPSC dependent on NMDAR
- Patient CSF



# Genetic Factors

## HLA-allele B\*07:02

- Encodes MHC class I peptides
  - Identifies non-self peptides to antigen-presenting cells
  - Expressed in phagocytes, B cells, and others



# Treatments

1. First-line immunotherapy (steroids, immunoglobulin, plasmapheresis, immunoadsorption) + removal of teratoma (if present)
2. Second-line immunotherapy: Rituximab, alemtuzumab (experimental)
3. Transcranial direct current stimulation as a treatment for associated cognitive disorders
4. Effectiveness of treatments varies from patient to patient

# Clinical Trials

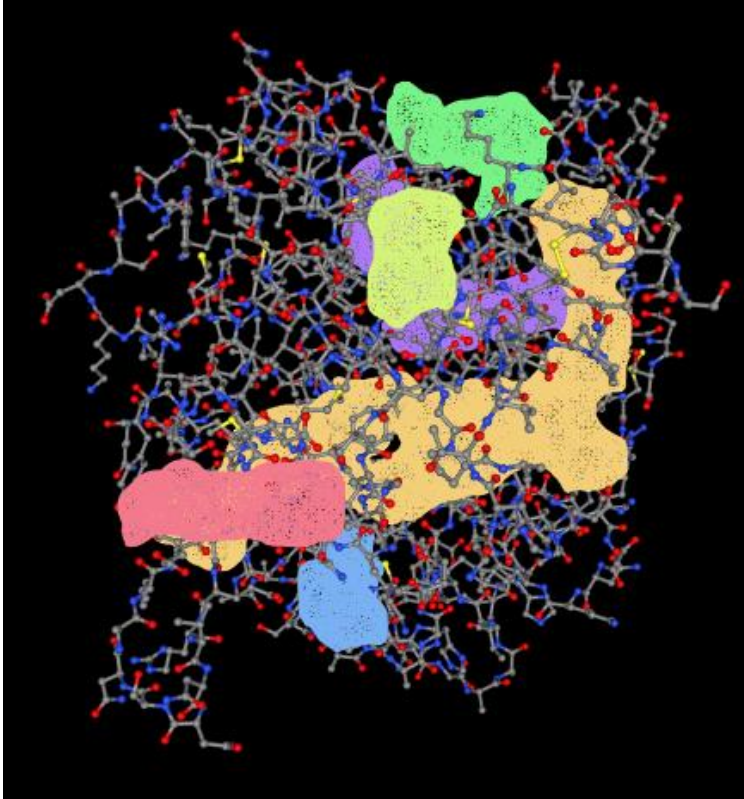
## **Immunoabsorption Therapy in Managing NMDAR Antibodies Encephalitis (IANMDAR)**

Cohort: 20, Intervention: Immunoabsorption therapy in conjunction with Rituximab

## **Transcranial Direct Current Stimulation on Cortical Plasticity in Patients With Anti-NMDA Receptor Encephalitis**

Cohort: 40, Intervention: Transcranial Direct Current Stimulation

# Future Directions



Left: Potential binding pockets on the NR1 subunit of the NMDA receptor

Spreading awareness of the disease

Determine the mechanism of action,  
genetic factors

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