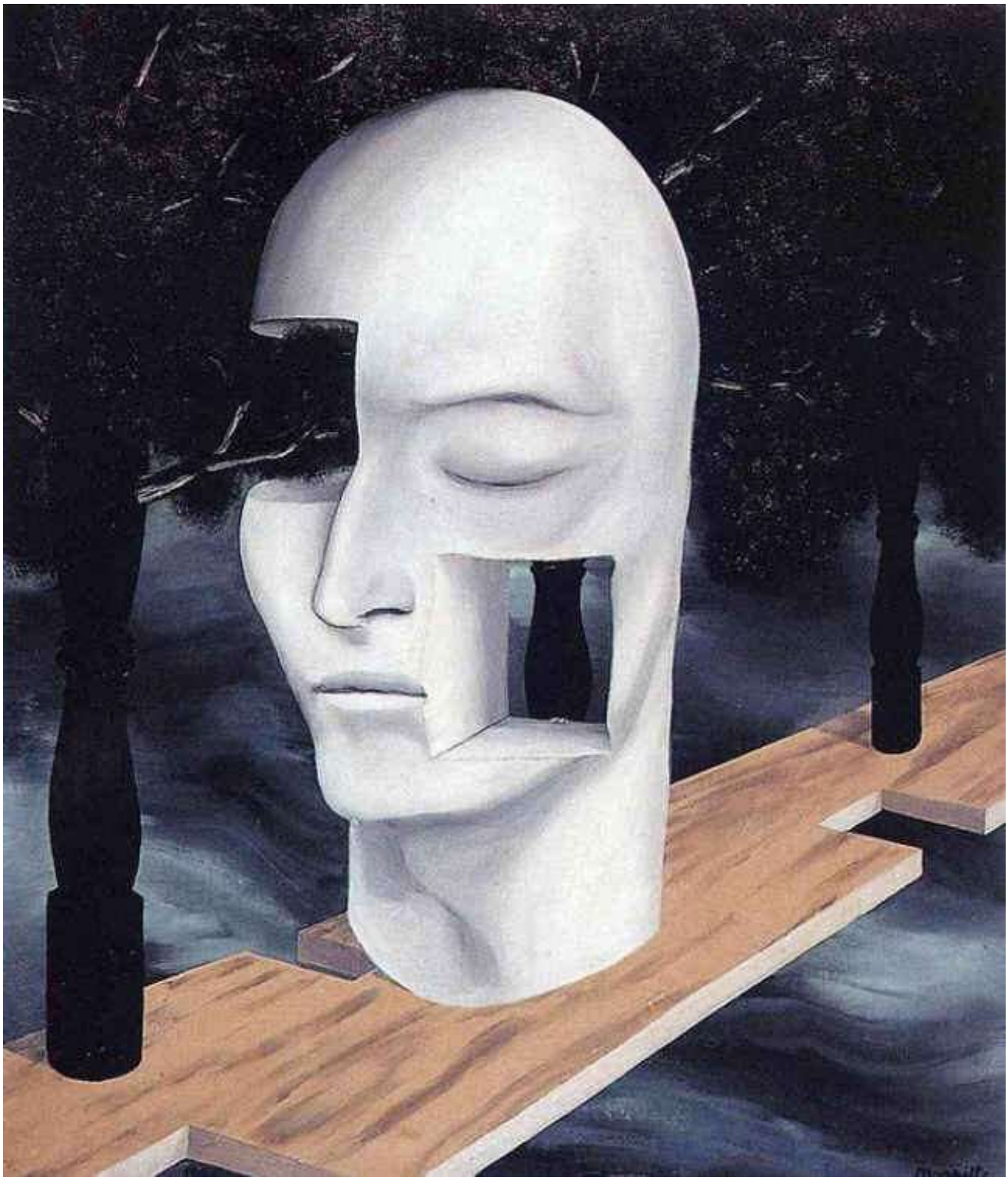
THE NORTHERN HOSPITAL

ENCEPHALITIS - ANTI-NMDA RECEPTOR



"The Face of Genius", oil on canvas, Rene Magritte

"Trying to understand the way nature works involves a most terrible test of human reasoning ability. It involves subtle trickery, beautiful tightropes of logic on which one has to walk in order not to make a mistake in predicting what will happen....."

We are at the very beginning of time for the human race. It is not unreasonable that we grapple with problems. But there are tens of thousands of years in the future. Our responsibility is to do what we can, learn what we can, improve the solutions, and pass them on.....

Richard P. Feynman

We are only at the beginning of time when it comes to understanding the human mind and the diseases which afflict it. As our understanding of autoimmune encephalitis advances, we may be nearer to understanding some causes of psychiatric illness which in the past and today utterly elude us. Our responsibility is to stand on the shoulders of giants who have gone before us, make our own small contributions towards progress, and to then pass these on to our future generations.

ENCEPHALITIS - ANTI-NMDA RECEPTOR

Introduction

Anti-NMDA receptor encephalitis is a severe, multistage, but treatable disorder presenting with prominent features of **psychosis**.

The presence of pronounced psychiatric symptoms often results in a misdiagnosis of functional psychosis or schizophrenia.

Diagnosis is vital as the condition, if untreated, is more likely to lead to severe and permeant neurological deficits or death.

This disease is most common in reproductive-aged (< 45 years) females.

There is a high association with ovarian teratoma, this being found in approximately 50% of cases of patients >18 years of age.

Early recognition is paramount as outcomes are better with early treatment.

However, as the disease is uncommon and only relatively recently described diagnosis is often not considered and so delayed.

Diagnosis is made by:

- **The detection of GluN1 or GluN2 antibodies within CSF**

Together with:

- **The clinical picture.**

Specific management consists of:

1. High-dose steroids
2. Intravenous immunoglobulin, (IVIG).
3. Plasma exchange
4. Immunosuppressants
5. Resection of any underlying neoplasm

With treatment *approximately*:

- 45% of patients have full recovery
- 30% have mild stable deficits
- 20% have severe deficits
- 5% of cases are lethal.

See also separate documents on

- **Encephalitis (in Infectious Diseases folder).**

History

Anti-NMDA receptor encephalitis is a neurologic disease first identified by **Dr. Josep Dalmau** and colleagues at the University of Pennsylvania in 2007.

Epidemiology

This disease is most common in reproductive-aged (< 45 years) females.

About 80% of cases are female.

It can however occur in children, males, and the elderly.

In one typical case series the mean age of patients was 23 years, but the range was 5 - 76 years. [2]

There is a high association with **ovarian teratoma**, this being found in approximately 50% of cases of patients >18 years of age.

Physiology

The **N-methyl-D-aspartate receptor** (also known as the **NMDA receptor** or **NMDAR**), is a glutamate / glycine receptor and ion channel protein found in central **neurones.**

It is one of the 4 types of i**o**notropic glutamate receptors, which include:

1. AMPA receptors
2. Delta receptors
3. Kainate receptors
4. NMDA receptors

The **NMDA** receptor forms a hetero-tetramer consisting of:

- 2 **GluN1** subunits (previously denoted as NR1)

And

- 2 **GluN2** subunits (previously denoted as NR2)

Glycine is a required *co-agonist* along with **glutamate** for activation of NMDA receptors.

Fascinatingly, the NMDA receptor is important for controlling "**synaptic plasticity**" and so is important for the ability of **memory**.

These receptors are especially prevalent in the **limbic system** and the **hippocampus**.

Pathophysiology

Encephalitis is an inflammatory condition of the brain which may essentially be

1. Infectious:

   See separate document - "Encephalitis" (in ID folder)

2. Autoimmune:

   There are 2 types of encephalitis that are immune mediated:

   - **Paraneoplastic encephalitis**:

     These are associated with antibodies against **intracellular neuronal proteins** (onco-neuronal proteins)

The paraneoplastic encephalitis syndromes are *invariably* **cancer related**

- **Autoimmune encephalitis:**

  These are associated with antibodies against neuronal **cell surface/synaptic proteins**.

  The autoimmune encephalitis syndromes may occur in the **presence** *or* **absence** of cancer.

Anti-NMDA receptor encephalitis is the **best characterized** of the autoimmune encephalitis syndromes and is associated with a predictable set of symptoms that combine to make up a **characteristic syndrome**.

In anti-NMDAR encephalitis, **auto-antibodies** bind to the NMDA receptor, leading to its internalization from the cell surface with resultant NMDA receptor loss of function.

NMDA receptor encephalitis is often associated with **ovarian teratomas**, however it can also occur in the apparent absence of a tumour.

The autoimmune mechanism may be due to "molecular mimicry" to neoplastic tissue (ovarian teratomas have been noted to have high rates of tissue positivity for the expression of NMDA receptors)

Alternatively a preceding **viral** or **bacterial infection** may trigger an autoantibody response to antigenic epitopes (or "antigenic determinant", i.e. the part of an antigen that is recognized by the immune system) located on the external surface of neuronal membranes, (in this case the NMDA receptor).

It should be noted that not all patients with detectable NMDA receptor autoantibodies get NMDA receptor encephalitis.

Incidental NMDA receptor antibody positivity has also been reported in other disease states.

Immunological Triggers:

Association with Teratoma:

Around 50% of women with anti-NMDA receptor encephalitis have an ovarian teratoma.

Accordingly one of the postulated mechanisms of Anti-NMDA receptor encephalitis is that neural type tissue found in the teratoma acts as an immunological trigger.

In this scenario, antigen released by apoptotic tumour cells is taken up by antigen presenting cells and then presented to the immunological system in the regional lymph nodes where memory B cells are generated that produce antibodies to neuronal components, (in this case the NMDA receptor).

Only 5% of men >18 years old have an identifiable tumor.

The younger a patient is, the less likely he or she is to have any associated tumor.

Other cancers have also been implicated as immunological triggers, including, small cell lung, thymoma, breast, and testicular cancers.

Overwhelmingly however, associated tumours are found to be ovarian teratomas.

Association with Herpes Simplex Virus:

Another postulated immunological trigger is Herpes Simplex viral antigens.

Approximately 20% of patients with Herpes simplex encephalitis develop antibodies against NMDA receptors.

Clinical features

Progressive and **rapidly worsening** *neuropsychiatric* symptoms is one strong clue to the diagnosis of Anti-NMDA receptor encephalitis.

Anti-NMDA receptor encephalitis appears to have discrete and often predictable phases of illness.

4 phases are recognized as follows: [4]

Phase 1, Prodrome:

Around 70% of patients experience a viral like prodrome, of non-specific "constitutional" symptoms, including:

1. Headache
2. Lethargy/ malaise
2. Fever
4. Myalgias
5. Nausea / vomiting.

Phase 2, Acute neuropsychiatric illness:

This is characterized by an alarming, rapidly progressive and highly variable psychiatric symptom cluster, followed by increasingly severe neurological deficits.

Given the frequent absence of hard neurologic symptoms during this period, patients are often first seen by a **psychiatrist**.

Features include:

Psychiatric Symptoms, (over weeks):

1. Anxiety/fear
2. Agitation/ restlessness.
3. Mood lability
4. Personality changes
5. **Psychotic** symptoms are prominent:
    - Delusional thought content
    - Hallucinations/ perceptual disturbances
    - Disorganized thoughts
    - Bizarre behaviours
6. Speech disturbances:

    Including:

    - Paucity
    - Mutism
    - Echolalia, (meaningless repetition of another person's words)
7. Short-term memory deficits and confusion:
    - Challenging to detect however, due to the severity of psychiatric symptoms).

Followed by:

Neurological deficits, (over months):

Patients can die during this phase or suffer from permeant neurological deficits.

1. Global alterations in consciousness:

- Decreased responsiveness
- Catatonic-like states.

2. Extrapyramidal type movement disorders:
   - Orofacial dyskinesias
   - Dystonic posturing
   - Choreic like movements
   - Muscle rigidity
3. Autonomic instability:
   - Hyperthermia:
     - ♥ For patients on neuroleptic drugs, Neuroleptic malignant syndrome may be considered.
   - Bradycardia or tachycardia.
   - Hypotension or hypertension
4. Seizures:
   - Seizures are partial motor or complex.
5. Hypoventilation, particularly in adults:
   - This seems to be central in origin and can be severe enough as to require prolonged (up to 2 months) mechanical ventilation.

Phase 3, Recovery/ Relapse :

The natural course of disease suggests some patients have a prolonged course of illness but **can then show spontaneous neurological improvement**

Recovery is variable and slow and hospitalization of around 3 - 4 months is usually required.

Autonomic and respiratory functions tend to normalize first, followed by resolution of movement abnormalities.

Cognitive and psychiatric disturbances are usually the slowest to improve, with frequent re-emergence of agitation and psychotic symptoms.

Phase 4, Persistent/ Permanent deficits:

Patients with anti-NMDA receptor encephalitis take considerable time to return to their baseline function, (many months to years).

Persistent / permanent deficits can include:

- Deficits in executive / cognitive function
- Behavioural abnormalities
- Abnormal sleep patterns

See also Appendix 2 below.

Prognosis:

Progressive neurologic deterioration and death can occur without treatment.

However, spontaneous recovery has also been described in a few patients after several months of severe symptoms

With treatment *approximately*:

- 45% of patients have full recovery
- 30% have mild stable deficits
- 20% have severe deficits
- 5% of cases are lethal.

Compared to other synaptic encephalitides, the relapse rate in anti-NMDA receptor encephalitis is relatively low, although it is still up to **25%.**

Differential diagnoses:

Important differential diagnoses will include:

1. Psychiatric illness
2. Other causes of encephalitis
    - Infective
    - Other autoimmune encephalopathies.
3. Toxic drug reactions

- Including Neuroleptic malignant syndrome

Investigations

The diagnosis is made by:

- The detection of GluN1 or GluN2 antibodies within CSF

Together with:

- The clinical picture.

Others investigations will be done to exclude other differential diagnoses or to look for secondary complications.

Blood tests:

For delirium / confusion in general, consider the following:

1. FBE
2. CRP
3. U&E/glucose
4. Ca/Mg/PO_4
5. LFTS
6. TFTs

Urine Drug Screen

This may be considered when the differential diagnosis of drug toxicity needs to be excluded.

CSF:

The diagnosis of anti-NMDA receptor encephalitis is confirmed by the detection of immunoglobulin G (**IgG**) neuronal antibodies to the **GluN1** or **GluN2** subunits of the **NMDA receptor** in **CSF**

CSF IgG antibody testing is highly sensitive and specific for anti-NMDA receptor encephalitis

False-positive and false negative results may occur when testing only for serum IgG.

CSF titers of anti-NMDA receptor antibodies correlate with clinical illness.

Both the synaptic effects and severity of symptoms are reversible with clearance of antibodies. Thus as with other *synaptic* encephalitides, the auto-antibodies themselves appear to be pathogenic.

The titer of **CSF** antibodies appears to correlate more closely with the clinical outcome than **serum** titers.

IgM and IgA antibodies against the NMDA receptor, which have been described in some patients with chronic schizophrenia or other chronic neurologic disorders, are **non-specific**, do not alter NMDA receptors in vivo, and have **no** additional value in the diagnosis of NMDA receptor encephalitis

CSF may also show the *non-specific* findings of:

- Lymphocytic pleocytosis.
- Oligoclonal bands (in around 60% of the cases).
- Elevated protein levels.

Note that at times LP is a problematic procedure in patients with significant agitation / confusion. Ketamine is sometimes required for adequate sedation for painful procedures in confused patients. In theoretical terms, ketamine, being an NMDA receptor blocker might be expected to aggravate the condition of NMDA receptor encephalitis - however in practice, "Ketamine and other sedatives when transiently used for LP or other short procedures do *not* seem to affect the course of the disease", (*personal communication, Dr Josep Dalmau, Adjunct Professor Neurology, University of Pennsylvania*).

EEG:

EEG is usually **abnormal**, showing:

- Slow and disorganized activity in the delta/theta range.
- Sometimes with superimposed electrographic seizures.

Pelvic Ultrasound:

For ovarian tumours.

CT Scan:

CT scan will usually be done in the initial work-up of patients, and is useful for excluding differential diagnoses, such as space occupying lesions.

Ovarian teratomas may be detected on CT scan (or MRI scan)

MRI:

Around 50% of patients have normal brain MRI scans.

Around 50% of patients show MRI abnormalities, including bilateral T2 or FLAIR signal hyper-intensities in:

- The medial temporal lobe, (most commonly within the hippocampus.
- Frontal cortex
- Cerebellar cortex
- Medulla oblongata
- Spinal cord

The presence of hippocampal lesions is the main predictor of poor prognosis in patients with anti-N-methyl-D-aspartate receptor encephalitis.

PET Scan:

This is not routinely performed.
However positron emission tomography reportedly shows characteristic increases in the frontal-occipital gradient of cerebral glucose metabolism. This has correlation with disease severity.

Management

General management:

General management involves:

1. Supportive measures as required:
    - In patients who develop hypoventilation, prolonged mechanical ventilation (weeks to months) may be required.
2. Seizures:
    - These are treated along conventional lines.
3. Psychiatric symptoms:
    - Control of **psychiatric** symptoms is very difficult.

High dose dopamine blockade may exacerbate dyskinetic and dystonic movements when used in an agitated patient, though it is unclear whether this stems from *excessive* blockade in what is often a neuroleptic naïve patient.

Drugs like haloperidol might further confound distinguishing anti-NMDA receptor encephalitis from NMS.

Highly sedating medications, such as **anticholinergics** and **benzodiazepines**, and **valproic acid** have proven helpful in many cases

Of the antipsychotic agents, those with more sedating effects such as quetiapine and chlorpromazine have been helpful. [4]

Specific Management:

Specific management/ options consist of:

1. High-dose steroids:

   - A regime of IV methylprednisolone 1 gram daily for 5 days in adults may be used. [1]

2. Intravenous immunoglobulin, (IVIG):

   - A regime of 400 mg/kg per day for 5 days

3. Plasma exchange

   - It is unknown whether IVIG and plasma exchange have similar efficacy.

     The use of plasma exchange is challenging in agitated / dyskinestic patients or patients with autonomic instability, and for this reason IVIG is often preferred.

4. Immunosuppressants

   In patients *without* an underlying tumor, first line immunotherapy (i.e. steroids and IVIG) is often not sufficient, and treatment with more potent immunosuppressants will be needed.

   Agents used include:

   - Cyclophosphamide

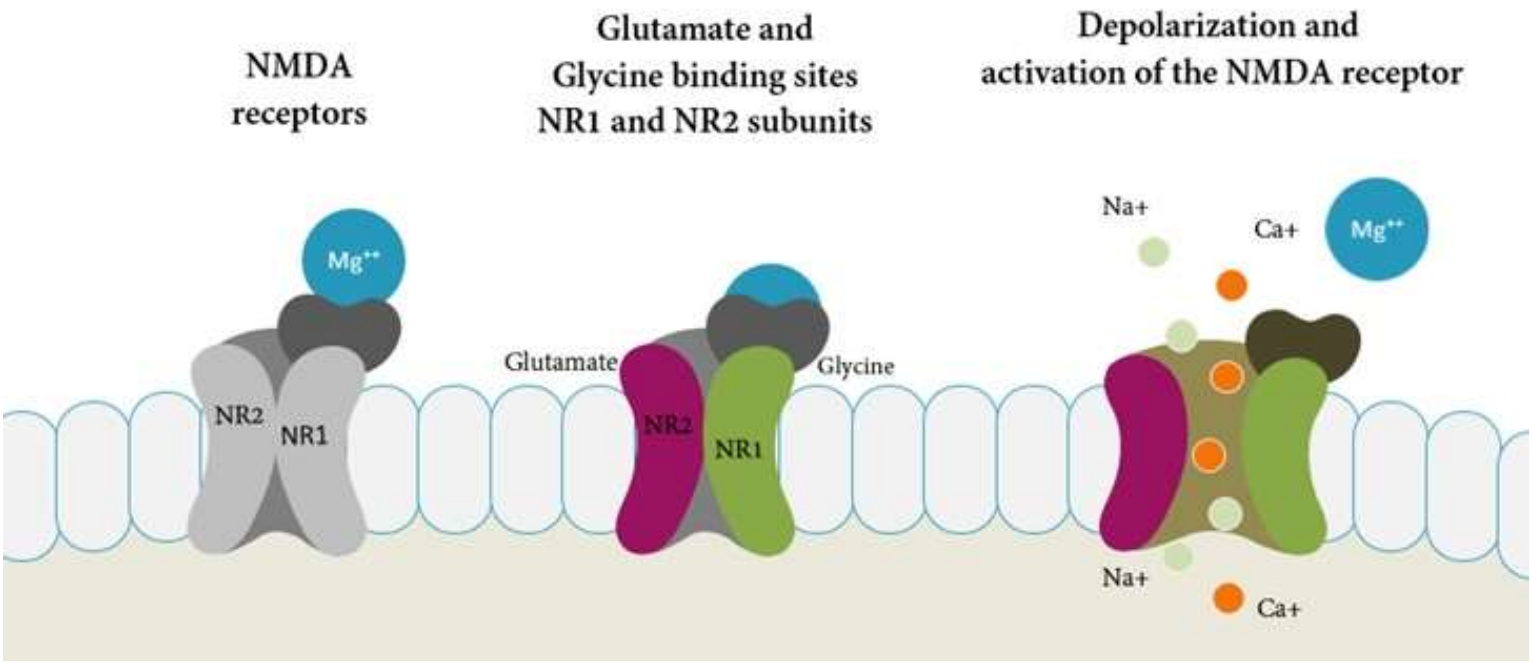
   - Rituximab

- ♥ Rituximab is a monoclonal antibody that depletes B cells from the circulation. It was originally used to treat lymphoma but is increasingly used for the treatment of autoimmune diseases.

5. Resection of any underlying neoplasm

This is an essential part of treatment.

Appendix 1: *The NMDA Receptor:*



Activation of the NMDA receptor:

Left: *NMDA receptor in the resting state, blocked with Mg.*

Middle: *Glutamate binding to NR2* ***and*** *glycine binding to NR1 results in ion channel opening.*

Right: *Mg is dislodged and sodium and calcium ions enter the neurone.*

The possible role of the NMDA receptor in psychosis and schizophrenia:

NMDA receptor antagonists, like phencyclidine, can mimic some of the symptoms of schizophrenia.

NMDA receptor has thus been implicated in the pathogenesis of schizophrenia in both its "positive" and "negative" symptoms. .

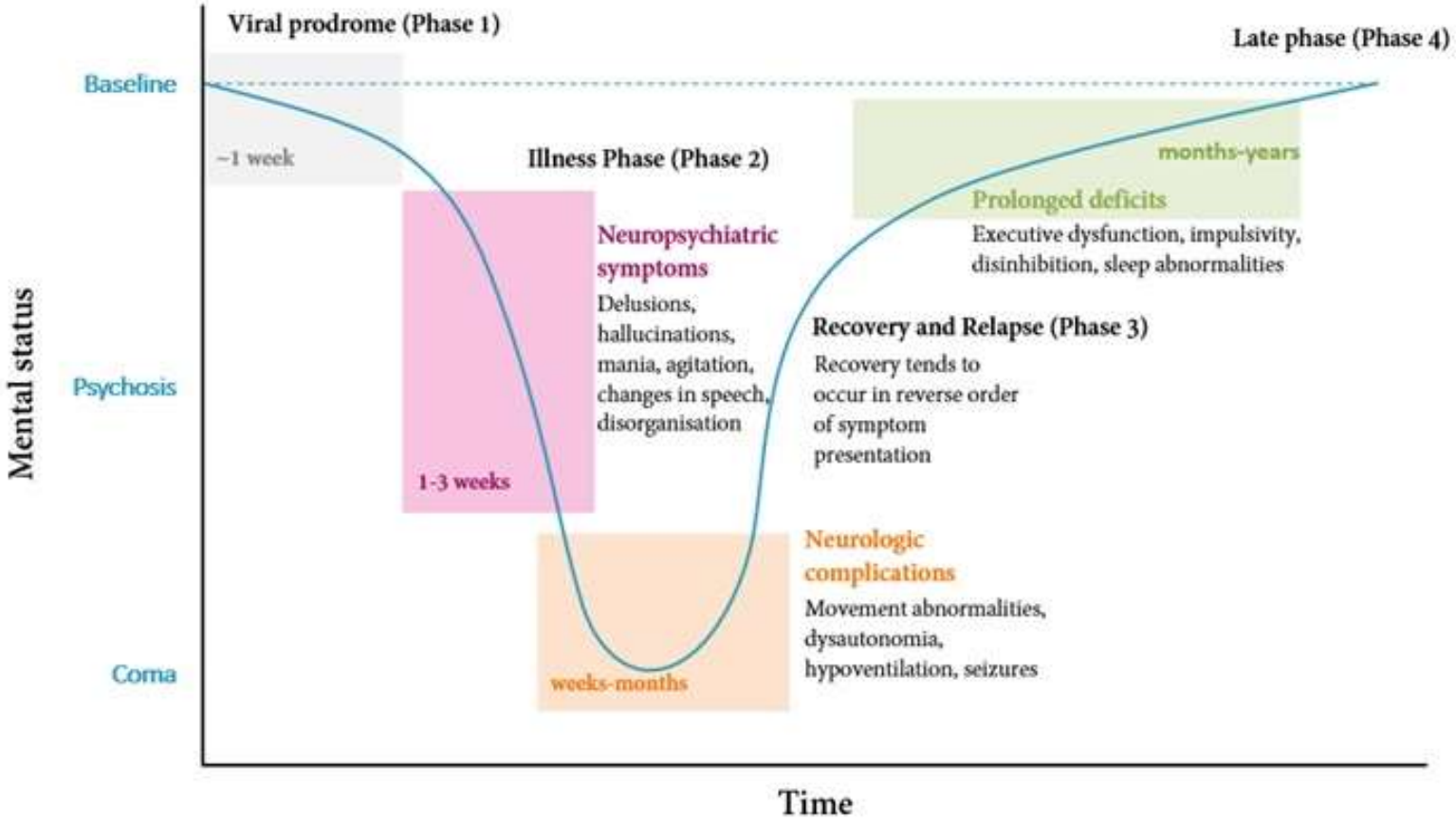
Normally, **excitatory** glutamate stimulates NMDA receptors in the interneuron resulting in GABA release from that neurone.

GABA, in turn, **inhibits** the release of **dopamine** within **mesolimbic** pathways.

Thus glutamatergic pathway can ultimately acts as a block on mesolimbic dopamine pathways.

If NMDA receptors are blocked, then the tonic inhibition of mesolimbic dopamine pathways is also ultimately blocked. This leads to elevated dopamine levels in the mesolimbic system and can result in schizophrenia-like symptoms.

Appendix 2



Typical clinical time course for Anti-NMDA receptor encephalitis, (from Kayser and Dalmau).

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18 July 2019.