

DETECTION OF AUTOANTIBODIES AGAINST NR1**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit and priority of U.S. Provisional Application No. 63/493,217, filed on March 30, 2023, which is incorporated by reference herein in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on March 26, 2024, is named 62548-705_601_SL.xml and is 68,612 bytes in size.

BACKGROUND

[0003] The N-methyl-D-aspartate receptor (NMDAR) is an ionotropic glutamate receptor that is known to be involved in a variety of functions in the central nervous system. It plays a crucial role in synaptic plasticity, long-term potentiation, and memory formation. NMDARs are activated upon binding of glycine and glutamate. Functional NMDARs are heterotetramers typically consisting of two NR1 subunits with either two of the four NR2 or two NR3 subunits. The glycine-binding modules of the NR1 and NR3 subunits and the glutamate-binding module of the NR2 subunit allow for precise control of ion permeability in physiologic conditions. Overactivation of NMDARs, causing excessive influx of Ca^{2+} into the neurons, can lead to excitotoxicity, which is known to occur in a multitude of neurological disorders such as Alzheimer disease, Parkinson, Epilepsy, and Huntington disease. On the other hand, hypofunction of NMDARs has been known to be associated with neuropsychiatric disorders, particularly psychosis and schizophrenia. NMDARs are also associated with a rare autoimmune disease, anti-NMDAR encephalitis. The anti-NMDAR encephalitis is characterized by psychiatric and neurological symptoms such as memory loss, hallucinations, delusions, and seizures. It is caused by the generation of Immunoglobulin G (IgG) autoantibodies against the NR1 subunit of NMDARs in the blood and in the brain. The anti-NMDAR autoantibodies induce the cross-linking and internalization of NMDARs. The reduced level of cell-surface NMDARs results in reduction of neuronal Ca^{2+} influx and decrease in synaptic currents, which causes several of the neuropsychiatric and neurological symptoms observed in patients.

SUMMARY

[0004] Currently, there is no established method to screen and/or detect anti-NMDAR autoantibody from blood samples and other easily acquired patient samples. Typical detection methods using an anti-NR1 antigen, such as enzyme-linked immunoassay (ELISA) or cell-based Fluorescence-activated cell sorting (FACS), require a high concentration of anti-NMDAR autoantibodies in sera/blood and therefore lack sensitivity. Lumbar puncture would be impractical to diagnose and study the psychiatric disorders associated with NMDARs. In addition, the level of anti-NMDAR autoantibodies in the cerebrospinal fluid (CSF) might still be below the threshold of these detection methods for disease with a lower concentration of anti-NMDAR autoantibodies or weaker affinity of anti-NMDAR autoantibodies. Described herein are compositions, methods, and systems for detecting a pathologic anti-NMDAR autoantibody in a biological sample of an individual. The advantage of this detection methods and systems is that it uses a plurality of non-randomized NMDAR antigens coupled to a solid support in unidirectional and density-controlled ways, which allows for a stronger binding avidity by two-arms of anti-NMDAR autoantibodies to the NMDAR antigens compared with conventional methods using randomly coated NMDAR antigens on a solid support. The disclosed detection methods and systems can detect the level of IgG/IgA/IgM anti-NMDAR autoantibodies in patients with either lower concentration and/or weaker affinity anti-NMDAR autoantibodies. In addition, this detection system can further be used to predict the treatment response to an antibody that blocks binding of a pathogenic antibody to NMDAR (e.g., ART5803).

[0005] Disclosed herein, in some aspects, is a plurality of N-methyl-D-aspartate receptor (NMDAR) antigens coupled to a solid support, wherein the plurality of NMDAR antigens are non-randomly coupled to the solid support.

[0006] In some embodiments, the solid support comprises a plate, a test tube, a microtiter well, a bead, a slide, a membrane, a microparticle, a nanoparticle, or a chip. In some embodiments, the solid support comprises plastic, derivatized plastic, polystyrene, polyvinyl chloride, a magnetic metal, a non-magnetic metal, glass, or silicon. In some embodiments, the plurality of NMDAR antigens comprise the amino acid sequence set forth in any of SEQ ID NOs: 1 to 5. In some embodiments, the plurality of NMDAR antigens comprise the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the plurality of NMDAR antigens comprise the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the plurality of NMDAR antigens comprise the amino acid sequence set forth in SEQ ID NO: 3. In some embodiments, the plurality of NMDAR antigens comprise the amino acid sequence set forth in SEQ ID NO: 4. In some embodiments, the plurality of NMDAR antigens comprise the amino acid sequence set forth in

SEQ ID NO: 5. In some embodiments, the plurality of NMDAR antigens lack an N-terminal signal peptide. In some embodiments, the plurality of NMDAR antigens do not comprise a GluN2A domain, GluN2B domain, GluN2C domain, GluN2D domain, or combinations thereof of NMDAR. In some embodiments, the plurality of NMDAR antigens are covalently coupled to the solid support. In some embodiments, the plurality of NMDAR antigens are noncovalently coupled to the solid support. In some embodiments, the plurality of NMDAR antigens further comprise an Fc polypeptide. In some embodiments, the Fc polypeptide is attached to the C-terminus of the plurality of NMDAR antigens. In some embodiments, the Fc polypeptide is attached to the N-terminus of the plurality of NMDAR antigens. In some embodiments, the plurality of antigens comprise an affinity tag. In some embodiments, the affinity tag comprises a His tag, a FLAG tag, a c-Myc tag, an HA tag, a V5 tag, a GST tag, a MBP tag, a CBP tag, a CBD tag, an Avi-tag, a biotinylated Avi-tag, or combinations thereof. In some embodiments, the affinity tag comprises a His tag. In some embodiments, the affinity tag comprises a biotinylated Avi-tag. In some embodiments, the biotinylated Avi-tag is coupled to a solid support comprising an avidin. In some embodiments, the avidin is deglycosylated avidin (e.g., neutravidin or streptavidin). In some embodiments, the affinity tag comprises a murine Fc tag.

[0007] In some embodiments, the affinity tag is coupled to the C-terminus of the plurality of NMDAR antigens. In some embodiments, the affinity tag is coupled to the N-terminus of the plurality of NMDAR antigens. In some embodiments, the murine Fc tag is non-covalently coupled to a solid support. In some embodiments, the His tag is non-covalently coupled to a solid support comprising nickel. In some embodiments, the solid support comprising nickel is a well of an enzyme-linked immunosorbent assay (ELISA) plate. In some embodiments, individual NMDAR antigens of the plurality of NMDAR antigens non-randomly coupled to the solid support are separated by an average distance of 15 nm or less. In some embodiments, the plurality of NMDAR antigens are bound to an anti-NMDAR antibody. In some embodiments, the plurality of NMDAR antigens are bound to a pathogenic anti-NMDAR antibody.

[0008] Disclosed herein, in some aspects, is a method of detecting a pathologic anti-NMDAR antibody in a biological sample of an individual, the method comprising contacting the biological sample of the individual to the plurality of NMDAR antigens of any one of the preceding embodiments, and detecting binding of the pathologic anti-NMDAR antibody in the biological sample to the plurality of NMDAR antigens.

[0009] In some embodiments, the biological sample comprises blood, plasma, serum, saliva, cell lysate, lymph, amniotic fluid, cerebral-spinal fluid, lachrymal fluid, mucus, urine, sputum, amniotic fluid, or sweat. In some embodiments, the biological sample comprises blood. In some embodiments, the biological sample comprises plasma. In some embodiments, the biological

sample comprises serum. In some embodiments, the biological sample comprises lymph. In some embodiments, the biological sample comprises cerebral-spinal fluid. In some embodiments, the biological sample comprises amniotic fluid. In some embodiments, the binding of the pathologic anti-NMDAR antibody to the plurality of NMDAR antigens is detected by an enzymatic reaction. In some embodiments, the binding of the pathologic anti-NMDAR antibody to the plurality of NMDAR antigens is detected by a fluorescent signal. In some embodiments, the binding of the pathologic anti-NMDAR antibody to the plurality of NMDAR antigens is detected by an immunoassay. In some embodiments, the immunoassay comprises an ELISA. In some embodiments, the ELISA comprises contacting the biological sample of the individual to the plurality of NMDAR antigens to produce a pathologic anti-NMDAR antibody/NMDAR antigen complex; and contacting the pathologic anti-NMDAR antibody/NMDAR antigen complex to a detection agent that binds to the pathologic anti-NMDAR antibody. In some embodiments, the detection agent is an anti-isotype antibody. In some embodiments, the detection agent is labeled with a fluorescent compound or an enzyme. In some embodiments, the binding of the pathologic anti-NMDAR antibody to the plurality of NMDAR antigens is detected by fluorescently activated cell sorting (FACS). In some embodiments, the anti-NMDAR antibody present in the biological sample is detected at a concentration of between 0.3 ng/mL - 100 µg/mL (e.g., 0.3-100 ng/mL). In some embodiments, the presence of the pathologic anti-NMDAR antibody indicates a diagnosis of autoimmune encephalitis, dementia, psychosis, schizophrenia, bipolar disorder, seizure, epilepsy, or depression. In some embodiments, the presence of the pathologic anti-NMDAR antibody indicates a diagnosis of autoimmune encephalitis. In some embodiments, the method further comprises quantifying a level of the pathologic anti-NMDAR antibody in the biological sample. In some embodiments, the method further comprises generating a report that indicates the presence of or the level of the anti-NMDAR antibody in the biological sample. In some embodiments, the method further comprises administering to the individual a therapeutic anti-NMDAR antibody or an anti-NMDAR binding fragment thereof that prevents binding of the pathologic anti-NMDAR autoantibody to an NMDAR of the individual, based upon detecting the presence of the pathologic anti-NMDAR antibody. In some embodiments, the therapeutic anti-NMDAR antibody comprises: a heavy chain variable region (VH) comprising: a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 13; a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 14; and/or a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 15; and a light chain variable region (VL) comprising: d) a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 16; e) a light chain complementary

determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 17; and/or f) a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 18. In some embodiments, the therapeutic anti-NMDAR antibody comprises: a heavy chain variable region (VH) comprising: a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 23; a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 24; and/or a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 25; and a light chain variable region (VL) comprising: d) a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 26; e) a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence EDN; and/or f) a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 28. In some embodiments, the therapeutic anti-NMDAR antibody comprises: a heavy chain variable region (VH) comprising: a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 33; a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 34; and/or a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 35; and a light chain variable region (VL) comprising: d) a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 36; e) a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 37; and/or f) a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 38. In some embodiments, the therapeutic anti-NMDAR antibody comprises: a heavy chain variable region (VH) comprising: a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 43; a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 44; and/or a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 45; and a light chain variable region (VL) comprising: d) a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 46; e) a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 47; and/or f) a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 48. In some embodiments, the therapeutic anti-NMDAR antibody comprises: a heavy chain variable region (VH) comprising: a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 53; a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 54; and/or a heavy chain

complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 55; and a light chain variable region (VL) comprising: d) a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 56; e) a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 57; and/or f) a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 58. In some embodiments, the therapeutic anti-NMDAR antibody comprises: a heavy chain variable region (VH) comprising: a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 63; a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 64; and/or a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 65; and a light chain variable region (VL) comprising: d) a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 66; e) a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 67; and/or f) a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 68. In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region and a light chain immunoglobulin variable region selected from: SEQ ID NO: 11 and SEQ ID NO: 12, SEQ ID NO: 21 and SEQ ID NO: 22, SEQ ID NO: 31 and SEQ ID NO: 32, SEQ ID NO: 41 and SEQ ID NO: 42, SEQ ID NO: 51 and SEQ ID NO: 52, or SEQ ID NO: 61 and SEQ ID NO: 62. In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 11 and a light chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 12. In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 11 and a light chain immunoglobulin variable region comprising an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 12. In some embodiments, the therapeutic anti-NMDAR antibody is a one-armed antibody. In some embodiments, detecting binding of the pathologic anti-NMDAR antibody in the biological sample comprises detecting binding of a IgG of the pathologic anti-NMDAR antibody. In some embodiments, detecting binding of the pathologic anti-NMDAR antibody in the biological sample comprises detecting binding of a IgA of the pathologic anti-NMDAR antibody. In some embodiments, detecting binding of the pathologic anti-NMDAR antibody in the biological sample comprises detecting binding of a IgM of the pathologic anti-NMDAR antibody. In some embodiments, detecting

binding of the pathologic anti-NMDAR antibody in the biological sample irrespective of whether the pathologic anti-NMDAR antibody in the biological sample is IgA, IgM, or IgG.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] The novel features described herein are set forth with particularity in the appended claims. A better understanding of the features and advantages of the features described herein will be obtained by reference to the following detailed description that sets forth illustrative examples, in which the principles of the features described herein are utilized, and the accompanying drawings of which:

[0011] **FIG. 1A** illustrates the random coating of NTD-NR1 on a plate and its binding of pathogenic autoantibody 102 Ab (two arms) and therapeutic antibody ART5803 (one arm).

[0012] **FIG. 1B** illustrates the non-randomized coating of NTD-NR1 with a His tag non-covalently coupled to a solid support comprising nickel and its binding of pathogenic autoantibody 102 Ab and therapeutic antibody ART5803.

[0013] **FIG. 2A** compares the binding affinity of pathogenic autoantibody 102 Ab and therapeutic antibody ART5803 on the NTD-NR1 random coating plate.

[0014] **FIG. 2B** compares the binding affinity of pathogenic autoantibody 102 Ab and therapeutic antibody ART5803 on the NTD-NR1 non-randomized coating plate.

[0015] **FIG. 3A** compares the binding affinity of pathogenic autoantibody 102 Ab and selected weak-affinity anti-NMDAR encephalitis monoclonal autoantibodies on the NTD-NR1 random coating plate.

[0016] **FIG. 3B** compares the binding affinity of pathogenic autoantibody 102 Ab and selected weak-affinity anti-NMDAR encephalitis monoclonal autoantibodies on the NTD-NR1 non-randomized coating plate.

[0017] **FIG. 4** illustrates that pathogenic anti-NMDAR autoantibody sensitive to therapeutic antibody ART5803 treatment can be displaceable by ART5803-Fab from NTD-NR1 on the NTD-NR1 non-randomized coating surface.

[0018] **FIG. 5** compares the dose dependent ART5803-Fab inhibition against pathogenic autoantibody 102 Ab and selected weak-affinity anti-NMDAR encephalitis monoclonal autoantibodies binding to NTD-NR1 on non-randomized coating surface.

[0019] **FIG. 6A** illustrates detection of various anti-NMDAR encephalitis monoclonal autoantibodies in serum using an exemplary NTD-NR1 non-randomized coating plate described herein.

[0020] **FIG. 6B** illustrates detection of various anti-NMDAR encephalitis monoclonal autoantibodies in another biological sample (cerebrospinal fluid (CSF)) using an exemplary NTD-NR1 non-randomized coating plate described herein.

[0021] **FIG. 7A** demonstrates that 102 Ab IgG, 102 Ab IgA, and 102 Ab IgM all display pathogenicity, as they induce significant internalization of NMDAR (NR1) in a cell-based assay.

[0022] **FIG. 7B** demonstrates that ART5803 blocks 102 Ab IgM induced NMDAR (NR1) internalization in a cell-based assay.

[0023] **FIG. 7C** demonstrates that ART5803 blocks 102 Ab IgA induced NMDAR (NR1) internalization in a cell-based assay.

[0024] **FIG. 7D** demonstrates that ART5803 blocks 102 Ab IgG induced NMDAR (NR1) internalization in a cell-based assay.

[0025] **FIG. 8A** illustrates detection of 102 Ab IgG, 102 Ab IgA, and 102 Ab IgM in serum using an exemplary NTD-NR1 non-randomized coating plate described herein.

[0026] **FIG. 8B** illustrates detection of 102 Ab IgG, 102 Ab IgA, and 102 Ab IgM in another biological sample (cerebrospinal fluid (CSF)) using an exemplary NTD-NR1 non-randomized coating plate described herein.

DETAILED DESCRIPTION

[0027] Described herein is a plurality of N-methyl-D-aspartate receptor (NMDAR) antigens coupled to a solid support, wherein the plurality of NMDAR antigens are non-randomly coupled to the solid support. The plurality of N-methyl-D-aspartate receptor (NMDAR) antigens coupled to the solid support may be contacted to a biological sample of an individual to screen for or diagnosis pathologies associated with pathogenic anti-NMDAR antigens.

Definitions

[0028] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the embodiments provided may be practiced without these details. Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” As used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise. Further,

headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed embodiments.

[0029] As used herein the term “NMDAR”, also known as N-methyl-D-aspartate receptor, NMDA receptor, refers to an ionotropic glutamate receptor and ion channel found in neurons. Ionotropic glutamate receptors are ligand-gated ion channels that allow rapid ion influx in response to glutamate. Both hyper- and hypo-functioning of NMDAR has been well documented to be related to neuropsychiatric and neurologic diseases.

[0030] As used herein the term “NR1,” or “NR1 subunit” refers to the NMDAR receptor NR1 subunit. For the purposes of this disclosure, the NR1 subunit comprises an amino acid sequence of SEQ ID NO: 6.

[0031] As used herein the term “NTD” refers to the N-terminal domain of the NMDAR receptor subunit. The NTD is an extracellular domain that is involved in assembly and channel modulation. As used herein the NTD is the NTD of the NR1 subunit. For the purposes of this disclosure, the NTD comprises an amino acid sequence set forth in any of SEQ ID NOs: 1 to 5. In certain cases the NTD lacks an N-terminal signal peptide.

[0032] As used herein the term “autoantibody,” or “autoantibodies” refers to an antibody from an organism, which is directed against a component of the same organism, or its binding site has a sequence that binds to an epitope from a protein from the same organism. As used herein the autoantibody is a human autoantibody. Pathogenic antibodies as described herein refer to antibodies that bind to NMDAR and induce internalization, reducing biological function of NMDAR, and decreasing the amount of NMDAR signaling in neurons. Such normal biological functions include activation by glutamate, glycine, or both and transport of cations including calcium.

[0033] As used herein “pathologic anti-NMDAR antibody” refers to an antibody that binds to NMDAR and induces a physiological state of disease, or predisposes an individual to develop a physiological state of disease. The physiological state of disease may include anti-NMDAR encephalitis, dementia, psychosis, schizophrenia, bipolar disorder, seizure, epilepsy, or depression.

[0034] As used herein the term “encephalitis” refers to an inflammation of the brain, with symptoms including reduced or alternation in consciousness, personality changes, psychotic delusions, rigidity, headache, fever, confusion, a stiff neck, and vomiting. Complications may include respiratory failure, seizures, hallucinations, trouble speaking, memory problems, and problems with hearing. As used herein the encephalitis is an anti-NMDAR encephalitis.

[0035] As used herein the term “ART5803” refers to an antibody, which may be a one-armed antibody, with a heavy and light chain variable region as set forth in SEQ ID NO: 11 and 12, respectively. This antibody is described in PCT Application No. WO2021241616A1.

[0036] As used herein the term “one armed antibody” differs from standard antibodies in that it is monovalent and comprises only a single binding moiety derived from a heavy and light chain variable region. Such one-armed antibodies may still comprise a constant region from either or both heavy and light chains, and further, may pair with a heavy chain that is not further coupled to a heavy chain variable region.

[0037] As used herein the term “about” refers to an amount that is near the stated amount by 10% or less.

[0038] As used herein the term “individual,” “patient,” or “subject” refers to individuals diagnosed with, suspected of being afflicted with, or at-risk of developing at least one disease for which the described compositions and method are useful for treating. In certain embodiments the individual is a mammal. In certain embodiments, the mammal is a mouse, rat, rabbit, dog, cat, horse, cow, sheep, pig, goat, llama, alpaca, or yak. In certain embodiments, the individual is a human.

[0039] Among the provided antibodies are monoclonal antibodies, multispecific antibodies (for example, and polyreactive antibodies), and antibody fragments. The antibodies include antibody-conjugates and molecules comprising the antibodies, such as chimeric molecules. Thus, an antibody includes, but is not limited to, full-length and native antibodies, as well as fragments and portion thereof retaining the binding specificities thereof, such as any specific binding portion thereof including those having any number of, immunoglobulin classes and/or isotypes (e.g., IgG1, IgG2, IgG3, IgG4, IgM, IgA, IgD, IgE and IgM); and biologically relevant (antigen-binding) fragments or specific binding portions thereof, including but not limited to Fab, F(ab')₂, Fv, and scFv (single chain or related entity). A monoclonal antibody is generally one within a composition of substantially homogeneous antibodies; thus, any individual antibodies comprised within the monoclonal antibody composition are identical except for possible naturally occurring mutations that may be present in minor amounts. The monoclonal antibody can comprise a human IgG1 constant region. The monoclonal antibody can comprise a human IgG4 constant region.

[0040] The term “antibody” herein is used in the broadest sense and includes monoclonal antibodies, and includes intact antibodies and functional (antigen-binding) antibody fragments thereof, including fragment antigen binding (Fab) fragments, F(ab')₂ fragments, Fab' fragments, Fv fragments, recombinant IgG (rIgG) fragments, single chain antibody fragments, including single chain variable fragments (sFv or scFv), and single domain antibodies (e.g., sdAb, sdFv,

nanobody) fragments. The term encompasses genetically engineered and/or otherwise modified forms of immunoglobulins, such as intrabodies, peptibodies, chimeric antibodies, fully human antibodies, humanized antibodies, and heteroconjugate antibodies, multispecific, e.g., bispecific, antibodies, diabodies, triabodies, and tetrabodies, tandem di-scFv, tandem tri-scFv. Unless otherwise stated, the term “antibody” should be understood to encompass functional antibody fragments thereof. The term also encompasses intact or full-length antibodies, including antibodies of any class or sub-class, including IgG and sub-classes thereof, IgM, IgE, IgA, and IgD. The antibody can comprise a human IgG1 constant region. The antibody can comprise a human IgG4 constant region.

[0041] For preparation of suitable antibodies, e.g., recombinant, monoclonal, or polyclonal antibodies, many techniques known in the art can be used (see, e.g., Kohler & Milstein, *Nature* 256:495-497 (1975); Kozbor et al., *Immunology Today* 4: 72 (1983); Cole et al., pp. 77-96 in *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc. (1985); Coligan, *Current Protocols in Immunology* (1991); Harlow & Lane, *Antibodies, A Laboratory Manual* (1988); and Goding, *Monoclonal Antibodies: Principles and Practice* (2d ed. 1986)). The genes encoding the heavy and light chains of an antibody of interest can be cloned from a cell, e.g., the genes encoding a monoclonal antibody can be cloned from a hybridoma and used to produce a recombinant monoclonal antibody. Gene libraries encoding heavy and light chains of monoclonal antibodies can also be made from hybridoma or plasma cells. Random combinations of the heavy and light chain gene products generate a large pool of antibodies with different antigenic specificity (see, e.g., Kuby, *Immunology* (3rd ed. 1997)). Techniques for the production of single chain antibodies or recombinant antibodies (U.S. Pat. Nos. 4,946,778, 4,816,567) can be adapted to produce antibodies of this disclosure. Also, transgenic mice, or other organisms such as other mammals, may be used to express humanized or human antibodies (see, e.g., U.S. Pat. Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, Marks et al., *Bio/Technology* 10:779-783 (1992); Lonberg et al., *Nature* 368:856-859 (1994); Morrison, *Nature* 368:812-13 (1994); Fishwild et al., *Nature Biotechnology* 14:845-51 (1996); Neuberger, *Nature Biotechnology* 14:826 (1996); and Lonberg & Huszar, *Intern. Rev. Immunol.* 13:65-93 (1995)). Alternatively, phage display technology can be used to identify antibodies and heteromeric Fab fragments that specifically bind to selected antigens (see, e.g., McCafferty et al., *Nature* 348:552-554 (1990); Marks et al., *Biotechnology* 10:779-783 (1992)). Antibodies can also be made bispecific, i.e., able to recognize two different antigens (see, e.g., WO 93/08829, Traunecker et al., *EMBO J.* 10:3655-3659 (1991); and Suresh et al., *Methods in Enzymology* 121:210 (1986)). Antibodies can also be heteroconjugates, e.g., two covalently joined antibodies, or immunotoxins (see, e.g., U.S. Pat. No. 4,676,980, WO 91/00360; WO 92/200373; and EP 03089).

[0042] The terms “complementarity determining region,” and “CDR,” which are synonymous with “hypervariable region” or “HVR,” are known in the art to refer to non-contiguous sequences of amino acid within antibody variable regions, which confer antigen specificity and/or binding affinity. In general, there are three CDRs in each heavy chain variable region (CDR-H1, CDR-H2, CDR-H3) and three CDRs in each light chain variable region (CDR-L1, CDR-L2, CDR-L3). “Framework regions” and “FR” are known in the art to refer to the non-CDR portions of the variable regions of the heavy and light chains. In general, there are four FRs in each full-length heavy chain variable region (FR-H1, FR-H2, FR-H3, and FR-H4), and four FRs in each full-length light chain variable region (FR-L1, FR-L2, FR-L3, and FR-L4). The precise amino acid sequence boundaries of a given CDR or FR can be readily determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (“Kabat” numbering scheme), Al-Lazikani et al., (1997) *JMB* 273,927-948 (“Chothia” numbering scheme); MacCallum et al., *J. Mol. Biol.* 262:732-745 (1996), “Antibody-antigen interactions: Contact analysis and binding site topography,” *J. Mol. Biol.* 262, 732-745.” (“Contact” numbering scheme); Lefranc MP et al., “IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains,” *Dev Comp Immunol*, 2003 Jan;27(1):55-77 (“IMGT” numbering scheme); Honegger A and Plückthun A, “Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis tool,” *J Mol Biol*, 2001 Jun 8;309(3):657-70, (“Aho” numbering scheme); and Whitelegg NR and Rees AR, “WAM: an improved algorithm for modelling antibodies on the WEB,” *Protein Eng.* 2000 Dec;13(12):819-24 (“AbM” numbering scheme. In certain embodiments, the CDRs of the antibodies described herein can be defined by a method selected from Kabat, Chothia, IMGT, Aho, AbM, or combinations thereof.

[0043] The boundaries of a given CDR or FR may vary depending on the scheme used for identification. For example, the Kabat scheme is based on structural alignments, while the Chothia scheme is based on structural information. Numbering for both the Kabat and Chothia schemes is based upon the most common antibody region sequence lengths, with insertions accommodated by insertion letters, for example, “30a,” and deletions appearing in some antibodies. The two schemes place certain insertions and deletions (“indels”) at different positions, resulting in differential numbering. The Contact scheme is based on analysis of complex crystal structures and is similar in many respects to the Chothia numbering scheme.

[0044] The term “variable region” or “variable domain” refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (V_H and V_L , respectively) of a native antibody generally have

similar structures, with each domain comprising four conserved framework regions (FRs) and three CDRs (*See e.g.*, Kindt et al. Kuby *Immunology*, 6th ed., W.H. Freeman and Co., page 91(2007)). A single V_H or V_L domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a V_H or V_L domain from an antibody that binds the antigen to screen a library of complementary V_L or V_H domains, respectively (*See e.g.*, Portolano et al., *J. Immunol.* 150:880-887 (1993); Clarkson et al., *Nature* 352:624-628 (1991)).

[0045] Specific binding or binding of antibody molecules described herein refers to binding mediated by one or more CDR portions of the antibody. Not all CDRs may be required for specific binding. Specific binding can be demonstrated for example by an ELISA against a specific recited target or antigen that shows significant increase in binding compared to an isotype control antibody.

[0046] As described herein an “epitope” refers to the binding determinant of an antibody or fragment described herein minimally necessary for specific binding of the antibody or fragment thereof to a target antigen. When the target antigen is a polypeptide the epitope will be a continuous or discontinuous epitope. A continuous epitope is formed by one region of the target antigen, while a discontinuous epitope may be formed from two or more separate regions. A discontinuous epitope, for example, may form when a target antigen adopts a tertiary structure that brings two amino acid sequences together and forms a three-dimensional structure bound by the antibody. When the target antigen is a polypeptide the epitope will generally be a plurality of amino acid linked into a polypeptide chain. A continuous epitope may comprise 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous amino acid. While an epitope may comprise a contiguous polymer of amino acid, not every amino acid of the polymer may be contacted by an amino acid residue of the antibody. Such non-contacted amino acids will still comprise part of the epitope as they may be important for the structure and linkage of the contacted amino acid. The skilled artisan may determine if any given antibody binds an epitope of a reference antibody, for example, by cross-blocking experiments with a reference antibody. In certain embodiments, described herein, are antibodies that bind the same epitope of the described antibodies. In certain embodiments, described herein, are antibodies that are competitively blocked by the described antibodies. In certain embodiments, described herein, are antibodies that compete for binding with the described antibodies.

[0047] Among the provided antibodies are antibody fragments. An “antibody fragment” refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include, but are not limited to, Fv, Fab, Fab', Fab'-SH, F(ab')₂; diabodies; linear antibodies;

single-chain antibody molecules (*e.g.* scFv or sFv); and multispecific antibodies formed from antibody fragments. In particular embodiments, the antibodies are single-chain antibody fragments comprising a variable heavy chain region and/or a variable light chain region, such as scFvs.

[0048] Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells. In some embodiments, the antibodies are recombinantly-produced fragments, such as fragments comprising arrangements that do not occur naturally, such as those with two or more antibody regions or chains joined by synthetic linkers, *e.g.*, polypeptide linkers, and/or those that are not produced by enzyme digestion of a naturally-occurring intact antibody. In some aspects, the antibody fragments are scFvs.

[0049] A “humanized” antibody is an antibody in which all or substantially all CDR amino acid residues are derived from non-human CDRs and all or substantially all FR amino acid residues are derived from human FRs. A humanized antibody optionally may include at least a portion of an antibody constant region derived from a human antibody. A “humanized form” of a non-human antibody refers to a variant of the non-human antibody that has undergone humanization, typically to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. In some embodiments, some FR residues in a humanized antibody are substituted with corresponding residues from a non-human antibody (*e.g.*, the antibody from which the CDR residues are derived), *e.g.*, to restore or improve antibody specificity or affinity.

[0050] Among the provided antibodies are human antibodies. A “human antibody” is an antibody with an amino acid sequence corresponding to that of an antibody produced by a human or a human cell, or non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences, including human antibody libraries. The term excludes humanized forms of non-human antibodies comprising non-human antigen-binding regions, such as those in which all or substantially all CDRs are non-human.

[0051] Human antibodies may be prepared by administering an immunogen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immunoglobulin loci, or which are present extrachromosomally or integrated randomly into the animal’s chromosomes. In such transgenic animals, the endogenous immunoglobulin loci have generally been inactivated. Human antibodies also may be derived from human antibody libraries, including

phage display and cell-free libraries, containing antibody-encoding sequences derived from a human repertoire.

[0052] The terms “polypeptide” and “protein” are used interchangeably to refer to a polymer of amino acid residues, and are not limited to a minimum length. Polypeptides, including the provided antibodies and antibody chains and other peptides, e.g., linkers and binding peptides, may include amino acid residues including natural and/or non-natural amino acid residues. The terms also include post-expression modifications of the polypeptide, for example, glycosylation, sialylation, acetylation, phosphorylation, and the like. In some aspects, the polypeptides may contain modifications with respect to a native or natural sequence, as long as the protein maintains the desired activity. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through mutations of hosts which produce the proteins or errors due to PCR amplification”. In some embodiments, amino acid sequence variants of the antibodies provided herein are contemplated. A variant typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants can be naturally occurring or can be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention and evaluating one or more biological activities of the polypeptide as described herein and/or using any of a number of known techniques. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, *e.g.*, antigen-binding.

[0053] Percent (%) sequence identity with respect to a reference polypeptide sequence is the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are known for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Appropriate parameters for aligning sequences are able to be determined, including algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence

identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, Calif., or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0054] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows: 100 times the fraction X/Y , where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0055] In some embodiments, an antibody provided herein has a dissociation constant (K_D) of about 1 μ M, 100 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 5 nM, 2 nM, 1 nM, 0.5 nM, 0.1 nM, 0.05 nM, 0.01 nM or less (*e.g.*, 10^{-8} M or less, *e.g.*, from 10^{-8} M to 10^{-13} M, *e.g.*, from 10^{-9} M to 10^{-13} M) for the antibody target. In some embodiments, an antibody provided herein has a dissociation constant (K_D) of about 100 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 5 nM, 2 nM, 1 nM, 0.5 nM, 0.1 nM, 0.05 nM, 0.01 nM, or 0.001 nM or greater (*e.g.*, 10^{-8} M or less, *e.g.*, from 10^{-8} M to 10^{-13} M, *e.g.*, from 10^{-9} M to 10^{-13} M) for the antibody target. The antibody target can be an NR1 target. K_D can be measured by any suitable assay. In certain embodiments, K_D can be measured using surface plasmon resonance assays (*e.g.*, using a BIACORE®-2000, a BIACORE®-3000 or Octet).

[0056] In some embodiments, an antibody provided herein may be further modified to contain additional nonproteinaceous moieties that are known and available. The moieties suitable for derivatization of the antibody include but are not limited to water soluble polymers. Non-limiting examples of water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran,

polyvinyl alcohol, polyvinyl pyrrolidone, poly-1,3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n vinyl pyrrolidone)polyethylene glycol, polypropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (*e.g.*, glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if two or more polymers are attached, they can be the same or different molecules.

[0057] The antibodies described herein can be encoded by a nucleic acid. A nucleic acid is a type of polynucleotide comprising two or more nucleotide bases. In certain embodiments, the nucleic acid is a component of a vector that can be used to transfer the polypeptide encoding polynucleotide into a cell. As used herein, the term “vector” refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a genomic integrated vector, or “integrated vector,” which can become integrated into the chromosomal DNA of the host cell. Another type of vector is an “episomal” vector, *e.g.*, a nucleic acid capable of extra-chromosomal replication. Vectors capable of directing the expression of genes to which they are operatively linked are referred to herein as “expression vectors.” Suitable vectors comprise plasmids, bacterial artificial chromosomes, yeast artificial chromosomes, viral vectors and the like. In the expression vectors regulatory elements such as promoters, enhancers, polyadenylation signals for use in controlling transcription can be derived from mammalian, microbial, viral or insect genes. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants may additionally be incorporated. Vectors derived from viruses, such as lentiviruses, retroviruses, adenoviruses, adeno-associated viruses, and the like, may be employed. Plasmid vectors can be linearized for integration into a genomic region. In certain embodiments, the expression vector is a plasmid. In certain embodiments, the expression vector is a lentivirus, adenovirus, or adeno-associated virus. In certain embodiments, the expression vector is an adenovirus. In certain embodiments, the expression vector is an adeno-associated virus. In certain embodiments, the expression vector is a lentivirus.

[0058] As used herein, the terms “homologous,” “homology,” or “percent homology” when used herein to describe to an amino acid sequence or a nucleic acid sequence, relative to a reference sequence, can be determined using the formula described by Karlin and Altschul (Proc. Natl. Acad. Sci. USA 87: 2264-2268, 1990, modified as in Proc. Natl. Acad. Sci. USA 90:5873-5877, 1993). Such a formula is incorporated into the basic local alignment search tool (BLAST)

programs of Altschul et al. (J. Mol. Biol. 215: 403-410, 1990). Percent homology of sequences can be determined using the most recent version of BLAST, as of the filing date of this application.

[0059] The nucleic acids encoding the antibodies described herein can be used to infect, transfect, transform, or otherwise render a suitable cell transgenic for the nucleic acid, thus enabling the production of antibodies for commercial or therapeutic uses. Standard cell lines and methods for the production of antibodies from a large scale cell culture are known in the art. *See e.g.*, Li et al., “Cell culture processes for monoclonal antibody production.” *Mabs*. 2010 Sep-Oct; 2(5): 466–477. In certain embodiments, the cell is a Eukaryotic cell. In certain embodiments, the Eukaryotic cell is a mammalian cell. In certain embodiments, the mammalian cell is a cell line useful for producing antibodies is a Chines Hamster Ovary cell (CHO) cell, an NS0 murine myeloma cell, or a PER.C6® cell. In certain embodiments, the nucleic acid encoding the antibody is integrated into a genomic locus of a cell useful for producing antibodies. In certain embodiments, described herein is a method of making an antibody comprising culturing a cell comprising a nucleic acid encoding an antibody under conditions *in vitro* sufficient to allow production and secretion of said antibody.

[0060] Also described herein are methods of making an antibody described herein. Such methods comprise incubating a cell or cell-line comprising a nucleic acid encoding the antibody in a cell culture medium under conditions sufficient to allow for expression and secretion of the antibody, and further harvesting the antibody from the cell culture medium. The harvesting can further comprise one or more purification steps to remove live cells, cellular debris, non-antibody proteins or polypeptides, undesired salts, buffers, and medium components. In certain embodiments, the additional purification step(s) include centrifugation, ultracentrifugation, protein A, protein G, protein A/G, or protein L purification, and/or ion exchange chromatography.

[0061] “Treat,” “treatment,” or “treating,” as used herein refers to, *e.g.*, a deliberate intervention to a physiological disease state resulting in the reduction in severity of a disease or condition; the reduction in the duration of a condition course; the amelioration or elimination of one or more symptoms associated with a disease or condition; or the provision of beneficial effects to a subject with a disease or condition. Treatment does not require curing the underlying disease or condition.

[0062] A “therapeutically effective amount,” “effective dose,” “effective amount,” or “therapeutically effective dosage” of a drug or therapeutic agent is any amount of the drug that, when used alone or in combination with another therapeutic agent, protects a subject against the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease

symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. The ability of a therapeutic agent to promote disease regression can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

[0063] As used herein, “pharmaceutically acceptable” with reference to a carrier “excipient” or “diluent” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. In some aspects, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g., by injection or infusion). Depending on the route of administration, the active compound, i.e., antibody, can be coated in a material to protect the compound from the action of acids and other natural conditions that can inactivate the compound.

[0064] The pharmaceutical compounds described herein can include one or more pharmaceutically acceptable salts. A “pharmaceutically acceptable salt” refers to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects (see e.g., Berge, S.M., et al. (1977) J. Pharm. Sci. 66: 1-19). Examples of such salts include acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl- substituted alkanolic acids, hydroxy alkanolic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N'-dibenzylethylenediamine, N-methylglucamine, chloroprocaine, choline, diethanolamine, ethylenediamine, procaine and the like.

Systems and Methods for detecting anti-NMDAR autoantibody

[0065] In one aspect, the disclosure provides a plurality of NMDAR antigens coupled to a support. In some embodiments, the plurality of NMDAR antigens are coupled non-randomly to the support.

[0066] In some embodiments, the support is a solid support comprising plastic, derivatized plastic, polystyrene, polyvinyl chloride, a magnetic metal, a non-magnetic metal, nickel, glass, or silicon. In some embodiments, the support is a partially solid support comprising a gel such as an agarose gel. In some embodiments, the solid support comprises nickel. In some embodiments, the

solid support comprises a plate, a test tube, a microtiter well, a bead, a slide, a membrane, a microparticle, a nanoparticle, or a chip.

[0067] In some embodiments, the plate comprises an 8 well plate, a 12 well plate, a 16 well plate, a 24 well plate, a 48 well plate, a 96 well plate, a 384 well plate, or a 1536 well plate. In some embodiments, the plate comprises a 96 well plate. In some embodiments, the plate comprises a 384 well plate. In some embodiments, the well shape of the plate comprises a flat bottom, a round bottom, a flat bottomed well with curved edges at the bottom, or a flat bottomed well with curved edges at the bottom with eight fins strategically placed at the bottom. In some embodiments, the color of the plate is clear, white, or black. Plates may be treated or derivatized, or not, to increase adsorption of polypeptides to their surfaces.

[0068] In some embodiments, the plate comprises an antibody-coated plate, an-antigen-coated plate, a streptavidin-coated plate, a NeutrAvidin™-coated plate, a nickel-coated plate, or a copper chelate-coated plate. In some embodiments, the material of the plate comprises plastic, derivatized plastic, polystyrene, polyvinyl chloride, glass, or silicon. In some embodiments, the surface of the plates is hydrophobic. In some embodiments, the surface of the plates is hydrophilic. Suitable plates to be used with the methods of this disclosure include Pierce™ Maleic Anhydride Activated Plates, Pierce™ Maleimide Activated Plates, Nunc™ CovaLink™ surface, Nunc™ NucleoLink™ Strips, or Nunc™ Amino™ Immobilizer Surface.

[0069] In some embodiments, the beads comprise nickel-coated beads, streptavidin-coated beads, NeutrAvidin™-coated beads, antibody-coated beads, paramagnetic beads, agarose beads, magnetic beads, electrostatic beads, electrically conducting beads, fluorescently labeled beads, colloidal beads, glass beads, semiconductor beads, or polymeric beads. In some embodiments, the material of the beads comprises magnetic, agarose, or glass. In some embodiments, the beads comprise nickel-coated beads.

[0070] The beads may be of a suitable diameter such that assays can be run using the beads including flow cytometry, immunoprecipitation, or the like.

[0071] In some embodiments, the diameter of the beads is at most about 1 μm, at most about 5 μm, at most about 10 μm, at most about 15 μm, at most about 20 μm, at most about 25 μm, at most about 30 μm, at most about 35 μm, at most about 40 μm, at most about 45 μm, at most about 50 μm, at most about 60 μm, at most about 70 μm, at most about 80 μm, at most about 90 μm, at most about 100 μm, at most about 150 μm, at most about 200 μm, at most about 250 μm, at most about 300 μm, at most about 350 μm, at most about 400 μm, at most about 450 μm, at most about 500 μm, at most about 600 μm, at most about 700 μm, at most about 800 μm, at most about 900 μm, or at most about 1000 μm.

[0072] In some embodiments, the diameter of the beads is at least about 1 μm , at least about 5 μm , at least about 10 μm , at least about 15 μm , at least about 20 μm , at least about 25 μm , at least about 30 μm , at least about 35 μm , at least about 40 μm , at least about 45 μm , at least about 50 μm , at least about 60 μm , at least about 70 μm , at least about 80 μm , at least about 90 μm , at least about 100 μm , at least about 150 μm , at least about 200 μm , at least about 250 μm , at least about 300 μm , at least about 350 μm , at least about 400 μm , at least about 450 μm , at least about 500 μm , at least about 600 μm , at least about 700 μm , at least about 800 μm , at least about 900 μm , or at least about 1000 μm .

[0073] In some embodiments, the diameter of the beads is about 1 μm , about 5 μm , about 10 μm , about 15 μm , about 20 μm , about 25 μm , about 30 μm , about 35 μm , about 40 μm , about 45 μm , about 50 μm , about 60 μm , about 70 μm , about 80 μm , about 90 μm , about 100 μm , about 150 μm , about 200 μm , about 250 μm , about 300 μm , about 350 μm , about 400 μm , about 450 μm , about 500 μm , about 600 μm , about 700 μm , about 800 μm , about 900 μm , or about 1000 μm .

[0074] In some embodiments, the diameter of the beads ranges from 1 to 1000 μm , 50 to 1000 μm , 100 to 1000 μm , 200 to 1000 μm , 300 to 1000 μm , 400 to 1000 μm , 500 to 1000 μm , 600 to 1000 μm , 700 to 1000 μm , 800 to 1000 μm , 900 to 1000 μm , 1 to 900 μm , 50 to 900 μm , 100 to 900 μm , 200 to 900 μm , 300 to 900 μm , 400 to 900 μm , 500 to 900 μm , 600 to 900 μm , 700 to 900 μm , 800 to 900 μm , 1 to 800 μm , 50 to 800 μm , 100 to 800 μm , 200 to 800 μm , 300 to 800 μm , 400 to 800 μm , 500 to 800 μm , 600 to 800 μm , 700 to 700 μm , 1 to 700 μm , 50 to 700 μm , 100 to 700 μm , 200 to 700 μm , 300 to 700 μm , 400 to 700 μm , 500 to 700 μm , 600 to 700 μm , 1 to 600 μm , 50 to 600 μm , 100 to 600 μm , 200 to 600 μm , 300 to 600 μm , 400 to 600 μm , 500 to 600 μm , 1 to 500 μm , 50 to 500 μm , 100 to 500 μm , 200 to 500 μm , 300 to 500 μm , 400 to 500 μm , 1 to 400 μm , 50 to 400 μm , 100 to 400 μm , 200 to 400 μm , 300 to 400 μm , 1 to 300 μm , 50 to 300 μm , 100 to 300 μm , 200 to 300 μm , 1 to 200 μm , 50 to 200 μm , 100 to 200 μm , 1 to 100 μm , 50 to 100 μm , or 1 to 50 μm .

[0075] In some embodiments, the chips comprise nickel-coated chips, streptavidin-coated chips, NeutrAvidin™-coated chips, antibody-coated chips, antigen-coated chips, microfluidic chips, or barcoded chips. In some embodiments, the material of the chips comprise ceramic, glass, plastic, derivatized plastic, polystyrene, polyvinyl chloride, gold, chemically inert metal, non-crosslinked carboxylated dextran hydrogel, alkyl derivatives of thiols, disulfides, thioethers, silanes, aminopropyltriethoxysilane, glycidylpropyltrimethoxysilane, or silicon. In some embodiments, the shape of the chip comprises stripes, rings, concentric rings, triangles, rectangles, polyhedrons, stars, cross-bars, letters, pictures on flat, convex, concaved, or irregular substrates.

[0076] Suitable chips to be used with the methods of this disclosure include Biacore™ Series S Sensor Chip Prisma, Biacore™ Series S Sensor Chip NA, Biacore™ Chip Protein L, Biacore™ Chip Protein G, Biacore™ Chip Protein A, Biacore™ Chip HPA, Biacore™ Chip CM7, Biacore™ Chip CM5, Biacore™ Chip CM4, Biacore™ Chip CM3, Biacore™ Chip C1, Biacore™ Chip Au, Octet® Streptavidin (SA) Biosensor, Octet® High Precision Streptavidin 2.0 (SAX2) Biosensors, Octet® Anti-Human Fc Capture (AHC) Biosensors, or Octet® Amine Reactive 2nd Generation (AR2G) Biosensors.

[0077] In some embodiments, antigens are spotted on the chips within a suitable spot diameter such that assays can be run using the chips to measure binding affinity, kinetic rate constants, thermodynamics, or the like.

[0078] In some embodiments, the spot diameter of the chips is at most about 0.1 μm , at most about 0.5 μm , at most about 1 μm , at most about 5 μm , at most about 10 μm , at most about 15 μm , at most about 20 μm , at most about 25 μm , at most about 30 μm , at most about 35 μm , at most about 40 μm , at most about 45 μm , at most about 50 μm , at most about 60 μm , at most about 70 μm , at most about 80 μm , at most about 90 μm , at most about 100 μm , at most about 150 μm , at most about 200 μm , at most about 250 μm , at most about 300 μm , at most about 350 μm , at most about 400 μm , at most about 450 μm , at most about 500 μm , at most about 600 μm , at most about 700 μm , at most about 800 μm , at most about 900 μm , or at most about 1000 μm .

[0079] In some embodiments, the spot diameter of the chips is at least about 0.1 μm , at least about 0.5 μm , at least about 1 μm , at least about 5 μm , at least about 10 μm , at least about 15 μm , at least about 20 μm , at least about 25 μm , at least about 30 μm , at least about 35 μm , at least about 40 μm , at least about 45 μm , at least about 50 μm , at least about 60 μm , at least about 70 μm , at least about 80 μm , at least about 90 μm , at least about 100 μm , at least about 150 μm , at least about 200 μm , at least about 250 μm , at least about 300 μm , at least about 350 μm , at least about 400 μm , at least about 450 μm , at least about 500 μm , at least about 600 μm , at least about 700 μm , at least about 800 μm , at least about 900 μm , or at least about 1000 μm .

[0080] In some embodiments, the spot diameter of the chips is about 0.1 μm , about 0.5 μm , about 1 μm , about 5 μm , about 10 μm , about 15 μm , about 20 μm , about 25 μm , about 30 μm , about 35 μm , about 40 μm , about 45 μm , about 50 μm , about 60 μm , about 70 μm , about 80 μm , about 90 μm , about 100 μm , about 150 μm , about 200 μm , about 250 μm , about 300 μm , about 350 μm , about 400 μm , about 450 μm , about 500 μm , about 600 μm , about 700 μm , about 800 μm , about 900 μm , or about 1000 μm .

[0081] In some embodiments, the spot diameter of the chips ranges from 0.1 to 1000 μm , 1 to 1000 μm , 50 to 1000 μm , 100 to 1000 μm , 200 to 1000 μm , 300 to 1000 μm , 400 to 1000 μm , 500 to 1000 μm , 600 to 1000 μm , 700 to 1000 μm , 800 to 1000 μm , 900 to 1000 μm , 0.1 to 900

μm, 1 to 900 μm, 50 to 900 μm, 100 to 900 μm, 200 to 900 μm, 300 to 900 μm, 400 to 900 μm, 500 to 900 μm, 600 to 900 μm, 700 to 900 μm, 800 to 900 μm, 0.1 to 800 μm, 1 to 800 μm, 50 to 800 μm, 100 to 800 μm, 200 to 800 μm, 300 to 800 μm, 400 to 800 μm, 500 to 800 μm, 600 to 800 μm, 700 to 800 μm, 0.1 to 700 μm, 1 to 700 μm, 50 to 700 μm, 100 to 700 μm, 200 to 700 μm, 300 to 700 μm, 400 to 700 μm, 500 to 700 μm, 600 to 700 μm, 0.1 to 600 μm, 1 to 600 μm, 50 to 600 μm, 100 to 600 μm, 200 to 600 μm, 300 to 600 μm, 400 to 600 μm, 500 to 600 μm, 0.1 to 500 μm, 1 to 500 μm, 50 to 500 μm, 100 to 500 μm, 200 to 500 μm, 300 to 500 μm, 400 to 500 μm, 0.1 to 400 μm, 1 to 400 μm, 50 to 400 μm, 100 to 400 μm, 200 to 400 μm, 300 to 400 μm, 0.1 to 300 μm, 1 to 300 μm, 50 to 300 μm, 100 to 300 μm, 200 to 300 μm, 0.1 to 200 μm, 1 to 200 μm, 50 to 200 μm, 100 to 200 μm, 0.1 to 100 μm, 1 to 100 μm, 50 to 100 μm, 0.1 to 50 μm, 1 to 50 μm, or 0.1 to 1 μm.

[0082] In some embodiments, the plurality of NMDAR antigens comprise a single epitope, a single NMDAR epitope, or a single NTD-NR1 epitope. In some embodiments, the NTD-NR1 epitope lacks an N-terminal signal peptide.

[0083] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 1.

[0084] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence of SEQ ID NO: 1. In some embodiments, the NTD-NR1 epitope lacks an N-terminal signal peptide.

[0085] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 1.

[0086] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 25, at least 30, at least 35, or at least 40 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 1.

[0087] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, at most 13, at most 14, at most 15, at most 16, at most 17, at most 18, at most 19, at most 20, at most 25, at most 30, at most 35, or at most 40 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 1.

[0088] In some embodiments, the NTD-NR1 epitope comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 1.

[0089] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0090] In certain embodiments, the NTD-NR1 epitope comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, or 40 contiguous amino acids from SEQ ID NO: 1.

[0091] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 2.

[0092] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence of SEQ ID NO: 2.

[0093] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 2.

[0094] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 25, or at least 30 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 2.

[0095] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, at most 13, at most 14, at most 15, at most 16, at most 17, at most 18, at most 19, at most 20, at most 25, or at most 30 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 2.

[0096] In some embodiments, the NTD-NR1 epitope comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, or 30 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 2.

[0097] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0098] In certain embodiments, the NTD-NR1 epitope comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, or 30 contiguous amino acids from SEQ ID NO: 2.

[0099] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 3.

[0100] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence of SEQ ID NO: 3.

[0101] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 3.

[0102] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 25 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 3.

[0103] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, at most 13, at most 14, at most 15, at most 16, at most 17, at most 18, at most 19, at most 20, or at most 25 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 3.

[0104] In some embodiments, the NTD-NR1 epitope comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 25 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 3.

[0105] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0106] In certain embodiments, the NTD-NR1 epitope comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 25 contiguous amino acids from SEQ ID NO: 3.

[0107] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 4.

[0108] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence of SEQ ID NO: 4.

[0109] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 4.

[0110] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 4.

[0111] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, at most 13, at most 14, at most 15, at most 16, at most 17, at most 18, at most 19, or at most 20 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 4.

[0112] In some embodiments, the NTD-NR1 epitope comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 4.

[0113] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0114] In certain embodiments, the NTD-NR1 epitope comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous amino acids from SEQ ID NO: 4.

[0115] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 5.

[0116] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence of SEQ ID NO: 5.

[0117] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 5.

[0118] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 5.

[0119] In some embodiments, the NTD-NR1 epitope comprises an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, at most 13, at most 14, at most 15, at most 16, at most 17, at most 18, at most 19, or at most 20 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 5.

[0120] In some embodiments, the NTD-NR1 epitope comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 5.

[0121] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0122] In certain embodiments, the NTD-NR1 epitope comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous amino acids from SEQ ID NO: 5.

[0123] In some embodiments, the plurality of NMDAR antigens further comprise a single Fc epitope. In some embodiments, the Fc epitope comprises an amino acid sequence with at least about 90%, at most least 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 100% sequence similarity to SEQ ID NO: 19.

[0124] In some embodiments, the Fc epitope comprises an amino acid sequence of SEQ ID NO: 19.

[0125] In some embodiments, the Fc epitope comprises an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 19.

[0126] In some embodiments, the Fc epitope comprises an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 19.

[0127] In some embodiments, the Fc epitope comprises an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, at most 13, at most 14, at most 15, at most 16, at most 17, at most 18, at most 19, or at most 20 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 19.

[0128] In some embodiments, the Fc epitope comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 19.

[0129] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0130] In certain embodiments, the Fc peptide comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 contiguous amino acids from SEQ ID NO: 19.

[0131] In some embodiments, the Fc peptide is attached to the C-terminus of the NMDAR. In some embodiments, the Fc peptide is attached to the N-terminus of the NMDAR.

[0132] In some embodiments, the plurality of NMDAR antigens do not comprise a GluN2A domain, GluN2B domain, GluN2C domain, GluN2D domain or combinations thereof of NMDAR.

[0133] In some embodiments, the plurality of NMDAR antigens are non-randomly coupled to the solid support by an affinity tag. In certain embodiments, the plurality of NMDAR antigens are non-randomly coupled to the solid support by non-affinity based method.

[0134] In some embodiments, the plurality of NMDAR antigens further comprise an affinity tag, wherein the affinity tag comprises a His tag, a FLAG tag, a c-Myc tag, an HA tag, a V5 tag, a GST tag, a MBP tag, a CBP tag, a CBD tag, an Avi-tag, a biotinylated Avi-tag, or combinations thereof.

[0135] In some embodiments, the affinity tag is coupled to the C-terminus of the NMDAR antigens. In some embodiments, the affinity tag is coupled to the N-terminus of the NMDAR antigen.

[0136] In some embodiments, the affinity tag comprises a His tag. An illustrative His tag sequence is set forth in SEQ ID NO: 70. In some embodiments, the His tag comprises a plurality of histidine residues for example, 6, 7, 8, 9, or 10 histidine residues. In some embodiments, the His tag is attached to the C-terminus of the NMDAR antigens. In some embodiments, the His tag is attached to the N-terminus of the NMDAR antigen. In some embodiments, the His tag is non-covalently coupled to the solid support comprising nickel. As non-limiting examples, His tag antibodies are commercially available from suppliers including Life Technologies, Pierce Antibodies, and GenScript.

[0137] In some embodiments, the affinity tag comprises a c-Myc tag. An illustrative c-Myc tag sequence is set forth in SEQ ID NO: 71. In some embodiments, the c-Myc tag is attached to the C-terminus of the NMDAR antigens. In some embodiments, the c-Myc tag is attached to the N-terminus of the NMDAR antigen. As non-limiting examples, c-Myc tag antibodies are commercially available from suppliers including Santa Cruz Biotechnology, Abcam, and Cell Signal.

[0138] In some embodiments, the affinity tag comprises a HA tag. An illustrative HA tag sequence is set forth in SEQ ID NO: 72. In some embodiments, the HA tag is attached to the C-terminus of the NMDAR antigens. In some embodiments, the HA tag is attached to the N-terminus of the NMDAR antigen. As non-limiting examples, HA tag antibodies are commercially available from suppliers including Pierce Antibodies, Cell Signal, and Abcam.

[0139] In some embodiments, the affinity tag comprises a V5 tag. An illustrative V5 tag sequence is set forth in SEQ ID NO: 73. In some embodiments, the V5 tag is attached to the C-terminus of the NMDAR antigens. In some embodiments, the V5 tag is attached to the N-

terminus of the NMDAR antigen. As non-limiting examples, V5 tag antibodies are commercially available from suppliers including Abcam, Thermo Fisher, and Sigma-Aldrich.

[0140] In some embodiments, the affinity tag comprises a GST tag. An illustrative GST tag sequence is set forth in SEQ ID NO: 74. In some embodiments, the GST tag is attached to the C-terminus of the NMDAR antigens. In some embodiments, the GST tag is attached to the N-terminus of the NMDAR antigen. As non-limiting examples, GST tag antibodies are commercially available from suppliers including Cube Biotech, Proteintech, and Sigma-Aldrich.

[0141] In some embodiments, the affinity tag comprises a MBP tag. An illustrative MBP tag sequence is set forth in SEQ ID NO: 75. In some embodiments, the MBP tag is attached to the C-terminus of the NMDAR antigens. In some embodiments, the MBP tag is attached to the N-terminus of the NMDAR antigen. As non-limiting examples, MBP tag antibodies are commercially available from suppliers including Thermo Fisher, OriGene, and Sigma-Aldrich.

[0142] In some embodiments, the affinity tag comprises a CBP tag. An illustrative CBP tag sequence is set forth in SEQ ID NO: 76. In some embodiments, the CBP tag is attached to the C-terminus of the NMDAR antigens. In some embodiments, the CBP tag is attached to the N-terminus of the NMDAR antigen. As non-limiting examples, CBP tag antibodies are commercially available from suppliers including Bioss Antibodies, GenScript, and Thermo Fisher.

[0143] In some embodiments, the affinity tag comprises a CBD tag. An illustrative CBD tag comprises an amino acid sequence as set forth in SEQ ID NO: 77. In some embodiments, the CBD tag is attached to the C-terminus of the NMDAR antigens. In some embodiments, the CBD tag is attached to the N-terminus of the NMDAR antigen. As non-limiting examples, CBD tag antibodies are commercially available from suppliers including New England Biolab and Abcam.

[0144] In some embodiments, the affinity tag comprises an Avi-tag. An illustrative Avi-tag comprises an amino acid sequence as set forth in SEQ ID NO: 78. In some embodiments, the Avi-tag comprises a biotinylated Avi-tag. In some embodiments, the Avi-tag is attached to the C-terminus of the NMDAR antigens. In some embodiments, the Avi tag is attached to the N-terminus of the NMDAR antigen. In some embodiments, the biotinylated Avi-tag is attached to the C-terminus of the NMDAR antigens. In some embodiments, the biotinylated Avi tag is attached to the N-terminus of the NMDAR antigen. As non-limiting examples, Avi tag antibodies are commercially available from suppliers including Pierce Antibodies, IsBio, and Genecopoeia.

[0145] In some embodiments, the affinity tag comprises a biotinylated Avi-tag and a His tag, for example, an Avi-tag disclosed herein and/or a His tag disclosed herein.

[0146] In some embodiments, the affinity tag comprises a Fc tag. An illustrative Fc tag sequence is set forth in SEQ ID NO: 81. In some embodiments, the Fc tag is attached to the C-

terminus of the NMDAR antigens. In some embodiments, the Fc tag is attached to the N-terminus of the NMDAR antigen. An illustrative sequence of a mouse Fc tag attached to the C-terminal of NR1-NTD is set forth in SEQ ID NO: 82. As non-limiting examples, Fc tag antibodies are commercially available from suppliers including Abcam, Thermo Fisher, and Sigma-Aldrich.

[0147] In some embodiments, individual NMDAR antigens of the plurality of NMDAR antigens non-randomly coupled to the solid support are separated by an average distance of at most about 25 nm or less, at most about 20 nm, at most about 15 nm, at most about 10 nm, at most about 5 nm, at most about 2 nm, or at most about 1 nm.

[0148] In some embodiments, individual NMDAR antigens of the plurality of NMDAR antigens non-randomly coupled to the solid support are separated by an average distance of at least about 25 nm, at least about 20 nm, at least about 15 nm, at least about 10 nm, at least about 5 nm, at least about 2 nm, or at least about 1 nm or more.

[0149] In some embodiments, individual NMDAR antigens of the plurality of NMDAR antigens non-randomly coupled to the solid support are separated by an average distance of about 25 nm, about 20 nm, about 15 nm, about 10 nm, about 5 nm, about 2 nm, or about 1 nm.

[0150] In some embodiments, individual NMDAR antigens of the plurality of NMDAR antigens non-randomly coupled to the solid support are separated by an average distance ranging from 1 to 20 nm, 2 to 20 nm, 5 to 20 nm, 10 to 20 nm, 15 to 20 nm, 1 to 18 nm, 2 to 18 nm, 5 to 18 nm, 10 to 18 nm, 15 to 18 nm, 1 to 15 nm, 2 to 15 nm, 5 to 15 nm, 10 to 15 nm, 1 to 10 nm, 2 to 10 nm, 5 to 10 nm, 1 to 5 nm, 2 to 5 nm, or 1 to 2 nm.

[0151] In some embodiments, the plurality of NMDAR antigens are non-randomly coupled to the solid support at a density of at most about 1000 ng/cm², at most about 900 ng/cm², at most about 800 ng/cm², at most about 700 ng/cm², at most about 600 ng/cm², at most about 500 ng/cm², at most about 400 ng/cm², at most about 300 ng/cm², at most about 200 ng/cm², at most about 100 ng/cm², at most about 90 ng/cm², at most about 80 ng/cm², at most about 70 ng/cm², at most about 60 ng/cm², at most about 50 ng/cm², at most about 40 ng/cm², at most about 30 ng/cm², at most about 20 ng/cm², at most about 10 ng/cm², at most about 5 ng/cm², at most about 2 ng/cm², or at most about 1 ng/cm².

[0152] In some embodiments, the plurality of NMDAR antigens are non-randomly coupled to the solid support at a density of at least about 1000 ng/cm², at least about 900 ng/cm², at least about 800 ng/cm², at least about 700 ng/cm², at least about 600 ng/cm², at least about 500 ng/cm², at least about 400 ng/cm², at least about 300 ng/cm², at least about 200 ng/cm², at least about 100 ng/cm², at least about 90 ng/cm², at least about 80 ng/cm², at least about 70 ng/cm², at least about 60 ng/cm², at least about 50 ng/cm², at least about 40 ng/cm², at least about 30

ng/cm², at least about 20 ng/cm², at least about 10 ng/cm², at least about 5 ng/cm², at least about 2 ng/cm², or at least about 1 ng/cm².

[0153] In some embodiments, the plurality of NMDAR antigens are non-randomly coupled to the solid support at a density of about 1000 ng/cm², about 900 ng/cm², about 800 ng/cm², about 700 ng/cm², about 600 ng/cm², about 500 ng/cm², about 400 ng/cm², about 300 ng/cm², about 200 ng/cm², about 100 ng/cm², about 90 ng/cm², about 80 ng/cm², about 70 ng/cm², about 60 ng/cm², about 50 ng/cm², about 40 ng/cm², about 30 ng/cm², about 20 ng/cm², about 10 ng/cm², about 5 ng/cm², about 2 ng/cm², or about 1 ng/cm².

[0154] In some embodiments, the plurality of NMDAR antigens are non-randomly coupled to the solid support at a density ranging from 1 to 1000 ng/cm², 2 to 1000 ng/cm², 5 to 1000 ng/cm², 10 to 1000 ng/cm², 20 to 1000 ng/cm², 30 to 1000 ng/cm², 40 to 1000 ng/cm², 50 to 1000 ng/cm², 60 to 1000 ng/cm², 70 to 1000 ng/cm², 80 to 1000 ng/cm², 90 to 1000 ng/cm², 100 to 1000 ng/cm², 200 to 1000 ng/cm², 300 to 1000 ng/cm², 400 to 1000 ng/cm², 500 to 1000 ng/cm², 600 to 1000 ng/cm², 700 to 1000 ng/cm², 800 to 1000 ng/cm², 900 to 1000 ng/cm², 1 to 900 ng/cm², 2 to 900 ng/cm², 5 to 900 ng/cm², 10 to 900 ng/cm², 20 to 900 ng/cm², 30 to 900 ng/cm², 40 to 900 ng/cm², 50 to 900 ng/cm², 60 to 900 ng/cm², 70 to 900 ng/cm², 80 to 900 ng/cm², 90 to 900 ng/cm², 100 to 900 ng/cm², 200 to 900 ng/cm², 300 to 900 ng/cm², 400 to 900 ng/cm², 500 to 900 ng/cm², 600 to 900 ng/cm², 700 to 900 ng/cm², 800 to 900 ng/cm², 1 to 800 ng/cm², 2 to 800 ng/cm², 5 to 800 ng/cm², 10 to 800 ng/cm², 20 to 800 ng/cm², 30 to 800 ng/cm², 40 to 800 ng/cm², 50 to 800 ng/cm², 60 to 800 ng/cm², 70 to 800 ng/cm², 80 to 800 ng/cm², 90 to 800 ng/cm², 100 to 800 ng/cm², 200 to 800 ng/cm², 300 to 800 ng/cm², 400 to 800 ng/cm², 500 to 800 ng/cm², 600 to 800 ng/cm², 700 to 800 ng/cm², 1 to 700 ng/cm², 2 to 700 ng/cm², 5 to 700 ng/cm², 10 to 700 ng/cm², 20 to 700 ng/cm², 30 to 700 ng/cm², 40 to 700 ng/cm², 50 to 700 ng/cm², 60 to 700 ng/cm², 70 to 700 ng/cm², 80 to 700 ng/cm², 90 to 700 ng/cm², 100 to 700 ng/cm², 200 to 700 ng/cm², 300 to 700 ng/cm², 400 to 700 ng/cm², 500 to 700 ng/cm², 600 to 700 ng/cm², 1 to 600 ng/cm², 2 to 600 ng/cm², 5 to 600 ng/cm², 10 to 600 ng/cm², 20 to 600 ng/cm², 30 to 600 ng/cm², 40 to 600 ng/cm², 50 to 600 ng/cm², 60 to 600 ng/cm², 70 to 600 ng/cm², 80 to 600 ng/cm², 90 to 600 ng/cm², 100 to 600 ng/cm², 200 to 600 ng/cm², 300 to 600 ng/cm², 400 to 600 ng/cm², 500 to 600 ng/cm², 1 to 500 ng/cm², 2 to 500 ng/cm², 5 to 500 ng/cm², 10 to 500 ng/cm², 20 to 500 ng/cm², 30 to 500 ng/cm², 40 to 500 ng/cm², 50 to 500 ng/cm², 60 to 500 ng/cm², 70 to 500 ng/cm², 80 to 500 ng/cm², 90 to 500 ng/cm², 100 to 500 ng/cm², 200 to 500 ng/cm², 300 to 500 ng/cm², 400 to 500 ng/cm², 1 to 400 ng/cm², 2 to 400 ng/cm², 5 to 400 ng/cm², 10 to 400 ng/cm², 20 to 400 ng/cm², 30 to 400 ng/cm², 40 to 400 ng/cm², 50 to 400 ng/cm², 60 to 400 ng/cm², 70 to 400 ng/cm², 80 to 400 ng/cm², 90 to 400 ng/cm², 100 to 400 ng/cm², 200 to 400 ng/cm², 300 to 400 ng/cm², 1 to 300 ng/cm², 2 to 300 ng/cm², 5 to 300

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[0155] In one aspect, the disclosure provides a method of detecting a pathologic anti-NMDAR antibody in a biological sample of an individual, wherein the method comprises contacting the biological sample of the individual to the plurality of NMDAR antigens described herein and detecting the binding of the pathologic anti-NMDAR antibody in the biological sample to the plurality of NMDAR antigens.

[0156] In some embodiments, the biological sample comprises blood, plasma, serum, saliva, cell lysate, lymph, amniotic fluid, cerebral-spinal fluid, lachrymal fluid, mucus, urine, sputum, amniotic fluid, or sweat. In some embodiments, the biological sample comprises plasma, serum, or cerebral spinal fluid. In some embodiments, the biological sample comprises blood, plasma, serum, lymph, cerebral-spinal fluid. In some embodiments, the biological sample comprises amniotic fluid. In some embodiments, the biological sample comprises blood. In some embodiments, the biological sample comprises plasma. In some embodiments, the biological sample comprises serum. In some embodiments, the biological sample comprises lymph. In some embodiments, the biological sample comprises cerebral-spinal fluid. In certain embodiments, the biological sample further comprises a diluent. In some embodiments, the biological sample comprises any suitable amount of a bodily fluid or tissue (e.g., blood, saliva, urine, skin or other

tissues) that may be collected from an individual. In some embodiments, the biological sample comprises a portion of an undiluted sample in a suitable diluent, for example, up to 50%, 40%, 30%, 20%, 10%, 5%, or 1% weight or volume of a sample included in an assay for anti-NMDAR antibodies.

[0157] In some embodiments, the binding of the pathologic anti-NMDAR antibody in the biological sample to the plurality of NMDAR antigens is detected by an enzymatic reaction. In some embodiments, the enzymatic reaction comprises an enzyme, wherein the enzyme comprises horseradish peroxidase enzyme (HRP), alkaline phosphatase (AP), beta-galactosidase (Gal), glucose oxidase, luciferase, beta-lactamase, urease or lysozyme. In some embodiments, the enzyme comprises HRP. In some embodiments, the enzyme comprises HRP and AP. In some embodiments, the enzymatic reaction comprises a substrate, wherein the substrate comprises TMB (3,3',5,5'-tetramethylbenzidine), ABTS (2,2'-Azinobis [3-ethylbenzothiazoline-6-sulfonic acid]-diammonium salt), OPD (o-phenylenediamine dihydrochloride), PNPP (p-Nitrophenyl Phosphate), ONPG (o-nitrophenyl- β -D-galactopyranoside), or AMPPD (adamantyl 1,2-dioxetane phenyl phosphate).

[0158] In some embodiments, the binding of the pathologic anti-NMDAR antibody in the biological sample to the plurality of NMDAR antigens is detected by a fluorescent signal. In some embodiments, the fluorescent signal is generated by a fluorophore, wherein the fluorophores comprises Alexa Fluor 350, Alexa Fluor 405, Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 555, Alexa Fluor 561, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 647, Alexa Fluor 660, Alexa Fluor 680, Alexa Fluor 700, Alexa Fluor 750, BODIPY FL, Coumarin, Cy3, Cy5, Fluorescein (FITC), Oregon Green, Pacific Blue, Pacific Green, Pacific Orange, PE-Cyanine7, PerCP-Cyanine5.5, Tetramethylrhodamine (TRITC), Texas Red, eFluor 450, eFluor 506, eFluor 660, PE-eFluor 610, PerCP-eFluor 710, APC-eFluor 780, Super Bright 436, Super Bright 600, Super Bright 645, Super Bright 702, Super Bright 780, Brilliant Ultra Violet Polymer Dyes, Brilliant Ultra Violet 395, Brilliant Ultra Violet 496, Brilliant Ultra Violet 563, Brilliant Ultra Violet 615, Brilliant Ultra Violet 661, Brilliant Ultra Violet 737, Brilliant Ultra Violet 805, Brilliant Violet 421, Brilliant Violet 480, Brilliant Violet 650, Brilliant Violet 711, Brilliant Violet 786, NovaFluor Blue 510 Dye, NovaFluor Blue 530 Dye, NovaFluor Blue 555 Dye, NovaFluor Blue 585 Dye, NovaFluor Blue 610-30S Dye, NovaFluor Blue 610-70S Dye, NovaFluor Blue 660-40S Dye, NovaFluor Blue 690, NovaFluor Blue 660-120S Dye, NovaFluor Yellow 570 Dye, NovaFluor Yellow 590 Dye, NovaFluor Yellow 610 Dye, NovaFluor Yellow 660 Dye, NovaFluor Yellow 690 Dye, NovaFluor Yellow 700 Dye, NovaFluor Yellow 730 Dye, NovaFluor Yellow 755, NovaFluor Red 660 Dye, NovaFluor Red

685 Dye, NovaFluor Red 700 Dye, NovaFluor Red 710 Dye, NovaFluor Red 725, or NovaFluor Red 755.

[0159] In some embodiments, the binding of the pathologic anti-NMDAR antibody in the biological sample to the plurality of NMDAR antigens can be detected by an immunoassay. In some embodiments, the immunoassay comprises an enzyme immunoassay, a radioimmunoassay, a fluoroimmunoassay, a chemiluminescent immunoassay, a counting immunoassay, an immunoenzymometric assay, an enzyme multiplied immunoassay technique, a photoacoustic Immunoassay, real-time immunoquantitative PCR, or an enzyme-linked immunosorbent assay (ELISA). In some embodiments, the immunoassay comprises an ELISA.

[0160] In some embodiments, the ELISA comprises contacting the biological sample of the individual to the plurality of NMDAR antigens to produce a pathologic anti-NMDAR antibody/NMDAR antigen complex; and contacting the pathologic anti-NMDAR antibody/NMDAR antigen complex to a detection agent that binds to the pathologic anti-NMDAR antibody.

[0161] In some embodiments, the detection agent comprises an antibody. In some embodiments, the antibody targets ART5803. In some embodiments, the antibody comprises an anti-isotype antibody. In some embodiments, the anti-isotype antibody comprises an antibody targeting IgA, IgD, IgG, IgE, or IgM. In some embodiments, the anti-isotype antibody comprises an antibody targeting IgA1, IgA2, IgD, IgG1, IgG2, IgG3, IgG4, IgE, or IgM. In some embodiments, the anti-isotype antibody comprises an antibody targeting IgA, IgG, or IgM. In some embodiments, the anti-isotype antibody comprises an antibody targeting IgG. In some embodiments, the anti-isotype antibody comprises an antibody targeting IgG1. In some embodiments, the anti-isotype antibody comprises an antibody targeting IgG2. In some embodiments, the anti-isotype antibody comprises an antibody targeting IgG3. In some embodiments, the anti-isotype antibody comprises an antibody targeting IgG4. In some embodiments, the anti-isotype antibody comprises an antibody targeting IgA. In some embodiments, the anti-isotype antibody comprises an antibody targeting IgA1. In some embodiments, the anti-isotype antibody comprises an antibody targeting IgA2. In some embodiments, the anti-isotype antibody comprises an antibody targeting IgM.

[0162] In some embodiments, the detection agent is labelled with a fluorescent tag, a radioactive tag, or an enzyme.

[0163] In some embodiments, the fluorescent tag comprises a fluorescent protein, wherein the fluorescent protein comprises a yellow fluorescent protein (YFP), a green fluorescent protein (GFP), a cyan fluorescent protein (CFP), a red fluorescent protein (RFP), umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine, fluorescein, cyanines,

dansyl chloride, phycocyanin, Venus, Citrine, mRuby3, mCherry, tdTomato, dsRed, phycoerythrin, or combinations thereof. In some embodiments, the fluorescent tag comprises a fluorophore disclosed herein.

[0164] In some embodiments, the radioactive tag comprises ^{32}P , ^{33}P , ^{47}Sc , ^{59}Fe , ^{64}Cu , ^{67}Cu , ^{75}Se , ^{77}As , ^{89}Sr , ^{90}Y , ^{99}Mo , ^{105}Rh , ^{109}Pd , ^{111}Ag , ^{125}I , ^{131}I , ^{142}Pr , ^{143}Pr , ^{149}Pm , ^{153}Sm , ^{161}Tb , ^{166}Ho , ^{169}Er , ^{177}Lu , ^{186}Re , ^{188}Re , ^{189}Re , ^{194}Ir , ^{198}Au , ^{199}Au , ^{211}Pb , ^{213}Bi , ^{58}Co , ^{67}Ga , $^{80\text{m}}\text{Br}$, $^{99\text{m}}\text{Tc}$, $^{193\text{m}}\text{Rh}$, ^{109}Pt , ^{111}In , ^{119}Sb , ^{125}I , ^{161}Ho , $^{189\text{m}}\text{Os}$, ^{192}Ir , ^{152}Dy , ^{211}At , ^{212}Bi , ^{223}Ra , ^{219}Rn , ^{215}Po , ^{211}Bi , ^{225}Ac , ^{221}Fr , ^{217}At , ^{213}Bi , ^{225}Fm , or combinations thereof.

[0165] In some embodiments, the enzyme comprises horseradish peroxidase enzyme (HRP), alkaline phosphatase (AP), beta-galactosidase (Gal), glucose oxidase, luciferase, beta-lactamase, urease, or lysozyme. In some embodiments, the enzyme comprises HRP. In some embodiments, the enzyme comprises HRP and AP.

[0166] In some embodiments, the binding of the pathologic anti-NMDAR antibody to the plurality of NMDAR antigens is detected by fluorescently activated cell sorting (FACS). In some embodiments, the FACS comprises contacting biological sample of the individual to the plurality of NMDAR antigens expressed in HEK cells to produce a pathologic anti-NMDAR antibody/NMDAR antigen complex; contacting the pathologic anti-NMDAR antibody/NMDAR antigen complex to a detection agent that binds to the pathologic anti-NMDAR antibody. In some embodiments, the detection agent is disclosed herein.

[0167] In some embodiments, the pathologic anti-NMDAR antibody present in the biological sample is detected at a concentration of at most about 500 $\mu\text{g/ml}$, at most about 400 $\mu\text{g/ml}$, at most about 300 $\mu\text{g/ml}$, at most about 200 $\mu\text{g/ml}$, at most about 100 $\mu\text{g/ml}$, at most about 90 $\mu\text{g/ml}$, at most about 80 $\mu\text{g/ml}$, at most about 70 $\mu\text{g/ml}$, at most about 60 $\mu\text{g/ml}$, at most about 50 $\mu\text{g/ml}$, at most about 40 $\mu\text{g/ml}$, at most about 30 $\mu\text{g/ml}$, at most about 20 $\mu\text{g/ml}$, at most about 10 $\mu\text{g/ml}$, at most about 5 $\mu\text{g/ml}$, at most about 2 $\mu\text{g/ml}$, or at most about 1 $\mu\text{g/ml}$ or more. In some embodiments, the pathologic anti-NMDAR antibody present in the biological sample is detected at a concentration of at most about 500 ng/ml , at most about 400 ng/ml , at most about 300 ng/ml , at most about 200 ng/ml , at most about 100 ng/ml , at most about 90 ng/ml , at most about 80 ng/ml , at most about 70 ng/ml , at most about 60 ng/ml , at most about 50 ng/ml , at most about 40 ng/ml , at most about 30 ng/ml , at most about 20 ng/ml , at most about 10 ng/ml , at most about 5 ng/ml , at most about 2 ng/ml , or at most about 1 ng/ml or more.

[0168] In some embodiments, the pathologic anti-NMDAR antibody present in the biological sample is detected at a concentration of at least about 500 ng/ml , at least about 400 ng/ml , at least about 300 ng/ml , at least about 200 ng/ml , at least about 100 ng/ml , at least about 90 ng/ml , at least about 80 ng/ml , at least about 70 ng/ml , at least about 60 ng/ml , at least about 50 ng/ml , at

least about 40 ng/ml, at least about 30 ng/ml, at least about 20 ng/ml, at least about 10 ng/ml, at least about 5 ng/ml, at least about 2 ng/ml, or at least about 1 ng/ml.

[0169] In some embodiments, the pathologic anti-NMDAR antibody present in the biological sample is detected at a concentration of about 500 ng/ml or less, about 400 ng/ml, about 300 ng/ml, about 200 ng/ml, about 100 ng/ml, about 90 ng/ml, about 80 ng/ml, about 70 ng/ml, about 60 ng/ml, about 50 ng/ml, about 40 ng/ml, about 30 ng/ml, about 20 ng/ml, about 10 ng/ml, about 5 ng/ml, about 2 ng/ml, or about 1 ng/ml. In some embodiments, the pathologic anti-NMDAR antibody present in the biological sample is detected at a concentration of about 500 µg/ml or less, about 400 µg/ml, about 300 µg/ml, about 200 µg/ml, about 100 µg/ml, about 90 µg/ml, about 80 µg/ml, about 70 µg/ml, about 60 µg/ml, about 50 µg/ml, about 40 µg/ml, about 30 µg/ml, about 20 µg/ml, about 10 µg/ml, about 5 µg/ml, about 2 µg/ml, or about 1 µg/ml.

[0170] In some embodiments, the pathologic anti-NMDAR antibody present in the biological sample is detected at a concentration ranging from 1 ng/ml to 500 µg/ml, 2 ng/ml to 500 µg/ml, 5 ng/ml to 500 µg/ml, 10 ng/ml to 500 µg/ml, 20 ng/ml to 500 µg/ml, 30 ng/ml to 500 µg/ml, 40 ng/ml to 500 µg/ml, 50 ng/ml to 500 µg/ml, 60 ng/ml to 500 µg/ml, 70 ng/ml to 500 µg/ml, 80 ng/ml to 500 µg/ml, 90 ng/ml to 500 µg/ml, 100 ng/ml to 500 µg/ml, or 200 ng/ml to 500 µg/ml. In some embodiments, the pathologic anti-NMDAR antibody present in the biological sample is detected at a concentration ranging from 1 to 500 ng/ml, 2 to 500 ng/ml, 5 to 500 ng/ml, 10 to 500 ng/ml, 20 to 500 ng/ml, 30 to 500 ng/ml, 40 to 500 ng/ml, 50 to 500 ng/ml, 60 to 500 ng/ml, 70 to 500 ng/ml, 80 to 500 ng/ml, 90 to 500 ng/ml, 100 to 500 ng/ml, 200 to 500 ng/ml, 300 to 500 ng/ml, 400 to 500 ng/ml, 1 to 400 ng/ml, 2 to 400 ng/ml, 5 to 400 ng/ml, 10 to 400 ng/ml, 20 to 400 ng/ml, 30 to 400 ng/ml, 40 to 400 ng/ml, 50 to 400 ng/ml, 60 to 400 ng/ml, 70 to 400 ng/ml, 80 to 400 ng/ml, 90 to 400 ng/ml, 100 to 400 ng/ml, 200 to 400 ng/ml, 300 to 400 ng/ml, 1 to 300 ng/ml, 2 to 300 ng/ml, 5 to 300 ng/ml, 10 to 300 ng/ml, 20 to 300 ng/ml, 30 to 300 ng/ml, 40 to 300 ng/ml, 50 to 300 ng/ml, 60 to 300 ng/ml, 70 to 300 ng/ml, 80 to 300 ng/ml, 90 to 300 ng/ml, 100 to 300 ng/ml, 200 to 300 ng/ml, 1 to 200 ng/ml, 2 to 200 ng/ml, 5 to 200 ng/ml, 10 to 200 ng/ml, 20 to 200 ng/ml, 30 to 200 ng/ml, 40 to 200 ng/ml, 50 to 200 ng/ml, 60 to 200 ng/ml, 70 to 200 ng/ml, 80 to 200 ng/ml, 90 to 200 ng/ml, 100 to 200 ng/ml, 1 to 100 ng/ml, 2 to 100 ng/ml, 5 to 100 ng/ml, 10 to 100 ng/ml, 20 to 100 ng/ml, 30 to 100 ng/ml, 40 to 100 ng/ml, 50 to 100 ng/ml, 60 to 100 ng/ml, 70 to 100 ng/ml, 80 to 100 ng/ml, 90 to 100 ng/ml, 1 to 90 ng/ml, 2 to 90 ng/ml, 5 to 90 ng/ml, 10 to 90 ng/ml, 20 to 90 ng/ml, 30 to 90 ng/ml, 40 to 90 ng/ml, 50 to 90 ng/ml, 60 to 90 ng/ml, 70 to 90 ng/ml, 80 to 90 ng/ml, 1 to 80 ng/ml, 2 to 80 ng/ml, 5 to 80 ng/ml, 10 to 80 ng/ml, 20 to 80 ng/ml, 30 to 80 ng/ml, 40 to 80 ng/ml, 50 to 80 ng/ml, 60 to 80 ng/ml, 70 to 80 ng/ml, 1 to 70 ng/ml, 2 to 70 ng/ml, 5 to 70 ng/ml, 10 to 70 ng/ml, 20 to 70 ng/ml, 30 to 70 ng/ml, 40 to 70 ng/ml, 50 to 70 ng/ml, 60 to 70 ng/ml, 1 to 60

ng/ml, 2 to 60 ng/ml, 5 to 60 ng/ml, 10 to 60 ng/ml, 20 to 60 ng/ml, 30 to 60 ng/ml, 40 to 60 ng/ml, 50 to 60 ng/ml, 1 to 50 ng/ml, 2 to 50 ng/ml, 5 to 50 ng/ml, 10 to 50 ng/ml, 20 to 50 ng/ml, 30 to 50 ng/ml, 40 to 50 ng/ml, 1 to 40 ng/ml, 2 to 40 ng/ml, 5 to 40 ng/ml, 10 to 40 ng/ml, 20 to 40 ng/ml, 30 to 40 ng/ml, 1 to 30 ng/ml, 2 to 30 ng/ml, 5 to 30 ng/ml, 10 to 30 ng/ml, 20 to 30 ng/ml, 1 to 20 ng/ml, 2 to 20 ng/ml, 5 to 20 ng/ml, 10 to 20 ng/ml, 1 to 10 ng/ml, 2 to 10 ng/ml, 5 to 10 ng/ml, 1 to 5 ng/ml, 2 to 5 ng/ml, or 1 to 2 ng/ml.

[0171] In some embodiments, the detection of the pathologic anti-NMDAR antibody indicates a diagnosis of an anti-NMDAR pathology. In some embodiments, the anti-NMDAR pathology comprises autoimmune encephalitis, anti-NMDAR autoimmune encephalitis, dementia, psychosis, schizophrenia, bipolar disorder, seizure, epilepsy, or depression. In some embodiments, the anti-NMDAR pathology comprises anti-NMDAR autoimmune encephalitis. In some embodiments, the anti-NMDAR pathology comprises dementia, psychosis, schizophrenia, bipolar disorder, seizure, epilepsy, or depression. In some embodiments, anti-NMDAR pathology comprises dementia. In some embodiments, anti-NMDAR pathology comprises psychosis. In some embodiments, anti-NMDAR pathology comprises schizophrenia. In some embodiments, anti-NMDAR pathology comprises bipolar disorder. In some embodiments, anti-NMDAR pathology comprises seizure. In some embodiments, anti-NMDAR pathology comprises epilepsy. In some embodiments, anti-NMDAR pathology comprises depression.

[0172] In some embodiments, the detection of the pathologic anti-NMDAR antibody is followed by administration of a therapeutic agent that treats an anti-NMDAR pathology. In some embodiments, the detection of the pathologic anti-NMDAR antibody is followed by administration of a therapeutic antibody that treats an anti-NMDAR pathology. In some embodiments, the detection of the pathologic anti-NMDAR antibody is followed by administration of a therapeutic anti-NMDAR antibody.

Therapeutic methods for disease associated with anti-NMDAR Autoantibody

[0173] The methods of detecting anti-NMDAR autoantibodies described herein can be combined with steps taken to treat an anti-NMDAR pathology.

[0174] In one aspect, disclosed herein is a therapeutic anti-NMDAR antibody or an anti-NMDAR binding fragment thereof that prevents binding of the pathologic anti-NMDAR autoantibody to an NMDA receptor of the individual, based upon detecting the presence of the pathologic anti-NMDAR antibody.

[0175] In some embodiments, the anti-NMDAR pathology comprises autoimmune encephalitis, anti-NMDAR autoimmune encephalitis, dementia, psychosis, schizophrenia, bipolar disorder, seizure, epilepsy, or depression. In some embodiments, the anti-NMDAR pathology

comprises anti-NMDAR autoimmune encephalitis. In some embodiments, the anti-NMDAR pathology comprises dementia, psychosis, schizophrenia, bipolar disorder, seizure, epilepsy, or depression. In some embodiments, anti-NMDAR pathology comprises dementia. In some embodiments, anti-NMDAR pathology comprises psychosis. In some embodiments, anti-NMDAR pathology comprises schizophrenia. In some embodiments, anti-NMDAR pathology comprises bipolar disorder. In some embodiments, anti-NMDAR pathology comprises seizure. In some embodiments, anti-NMDAR pathology comprises epilepsy. In some embodiments, anti-NMDAR pathology comprises depression.

[0176] Treatment refers to a method that seeks to partially or completely alleviating, ameliorating, relieving, delaying onset of, inhibiting, or slowing progression of, reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular disease, disorder, and/or condition being treated. The treatment of anti-NMDAR autoimmune encephalitis by a therapeutic anti-NMDAR antibody or an anti-NMDAR binding fragment thereof is expected to produce significant improvement in one or more of the typical clinical presentations such as improvement in acute psychiatric symptoms, improved memory function, reductions in seizures or dyskinesias, and improvement in consciousness and awareness. Various measures and tools for assessing psychiatric states are well-known to a clinician trained in the field. In some embodiments, clinical improvement before and/or after treatment is determined by the treating physician using the clinical global impression (CGI) generally as a summary measure for severity (CGI-S) and improvement (CGI-I). In some embodiments, after treatment, CGI reflects improvement on mental state. In some embodiments, after treatment, CGI is much improved. In some embodiments, after treatment, CGI is very much improved.

[0177] In some embodiments, clinical improvement in terms of functional recovery before and/or after treatment is evaluated using the modified Rankin Scale (mRS), with improvement in mRS scores obtained after treatment. In some embodiments, after treatment, mRS is 4 or lower. In some embodiments, after treatment, mRS is 3 or lower. In some embodiments, after treatment, mRS is 2 or lower. In some embodiments, after treatment, mRS is 1 or lower. In some embodiments, after treatment, mRS is 0. In some embodiments, an individual receiving treatment will score 1, 2, 3, 4, 5, or 6 points lower compared to a pretreatment assessment.

[0178] In some embodiments, clinical improvement for cognitive assessment before and/or after treatment is conducted by monitoring Montreal Cognitive Assessment scores (MOCA), with increases in MOCA scores obtained with treatment. In some embodiments, after treatment, MOCA reflects normal cognitive function. In some embodiments after treatment, MOCA is 27 or higher. In some embodiments, after treatment, MOCA is 26 or higher. In some embodiments after treatment, MOCA is 25 or higher. In some embodiments, after treatment, MOCA is 24 or

higher. In some embodiments, after treatment, MOCA is 23 or higher. In some embodiments, after treatment, MOCA is 22 or higher. In some embodiments, after treatment, MOCA is 21 or higher. In some embodiments, after treatment, MOCA is 20 or higher. In some embodiments, after treatment, MOCA is 19 or higher. In some embodiments, after treatment, MOCA is 18 or higher. In some embodiments, an individual receiving treatment will score 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 points higher compared to a pretreatment assessment.

[0179] In some embodiments, clinical improvement for patients with seizures before and/or after treatment is demonstrated by a decrease in the number of seizures after treatment. In some embodiments, after treatment, the number of seizures is decreased by 90% or more. In some embodiments, after treatment, the number of seizures is decreased by 80% or more. In some embodiments, after treatment, the number of seizures is decreased by 70% or more. In some embodiments, after treatment, the number of seizures is decreased by 60% or more. In some embodiments, after treatment, the number of seizures is decreased by 50% or more. In some embodiments, after treatment, the number of seizures is decreased by 40% or more. In some embodiments, after treatment, the number of seizures is decreased by 30% or more. In some embodiments, after treatment, the number of seizures is decreased by 20% or more. In some embodiments, after treatment, the number of seizures is decreased by 10% or more. In some embodiments, after treatment, the number of seizures is decreased by 5% or more.

[0180] In some embodiments, clinical improvement for dyskinesia symptoms before and/or after treatment is evaluated using Abnormal Involuntary Movement Scale (AIMS), the Unified Parkinson's Disease Rating Scale (UPDRS) part IV, the Obeso Dyskinesia Rating Scale, the Rush Dyskinesia Rating Scale, the Clinical Dyskinesia Rating Scale (CDRS), the Lang-Fahn Activities of Daily Living Dyskinesia Scale, the Parkinson Disease Dyskinesia Scale (PDYS-26), and the Unified Dyskinesia Rating Scale (UDysRS). In some embodiments, after treatment, the dyskinesia symptoms are improved from severe to moderate. In some embodiments, after treatment, the dyskinesia symptoms are improved from severe to mild. In some embodiments, after treatment, the dyskinesia symptoms are improved from severe to minimal. In some embodiments, after treatment, the dyskinesia symptoms are improved from severe to none. In some embodiments, after treatment, the dyskinesia symptoms are improved from moderate to mild. In some embodiments, after treatment, the dyskinesia symptoms are improved from moderate to minimal. In some embodiments, after treatment, the dyskinesia symptoms are improved from moderate to none. In some embodiments, after treatment, the dyskinesia symptoms are improved from mild to minimal. In some embodiments, after treatment, the dyskinesia symptoms are improved from mild to none. In some embodiments, after treatment, the dyskinesia symptoms are improved from minimal to none.

[0181] In some embodiments, clinical improvement for memory loss before and/or after treatment is evaluated using tests such as Mini-cognition tests and Mini Mental State Exam (MMSE) after treatment. In some embodiments, after treatment, MMSE reflects normal cognitive function. In some embodiments, after treatment, MOCA is 29 or higher. In some embodiments, after treatment, MOCA is 28 or higher. In some embodiments, after treatment, MOCA is 27 or higher. In some embodiments, after treatment, MOCA is 26 or higher. In some embodiments, after treatment, MOCA is 25 or higher. In some embodiments, after treatment, MOCA is 24 or higher. In some embodiments, after treatment, MOCA is 23 or higher. In some embodiments, after treatment, MOCA is 22 or higher. In some embodiments, after treatment, MOCA is 21 or higher. In some embodiments, after treatment, MOCA is 20 or higher. In some embodiments, after treatment, MOCA is 19 or higher. In some embodiments, an individual receiving treatment will score 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 points or higher compared to a pretreatment assessment.

[0182] In some embodiments, clinical improvement for Schizophrenia before and/or after treatment is evaluated using the Positive and Negative Symptom Scale (PANSS) total score, the positive symptom sub-scale score of the PANSS, the negative symptom sub-scale score of the PANSS, the general psychopathology sub-scale of the PANSS, the Brief Psychiatric Rating Scale (BPRS) total score derived from the PANSS, the BPRS psychosis derived from the PANSS, or any combination thereof. In some embodiments, after treatment, PANSS total score is reduced by 90% or more. In some embodiments, after treatment, PANSS total score is reduced by 80% or more. In some embodiments, after treatment, PANSS total score is reduced by 70% or more. In some embodiments, after treatment, PANSS total score is reduced by 60% or more. In some embodiments, after treatment, PANSS total score is reduced by 50% or more. In some embodiments, after treatment, PANSS total score is reduced by 40% or more. In some embodiments, after treatment, PANSS total score is reduced by 30% or more. In some embodiments, after treatment, PANSS total score is reduced by 20% or more. In some embodiments, after treatment, PANSS total score is reduced by 10% or more. In some embodiments, after treatment, PANSS total score is reduced by 5% or more. In some embodiments, after treatment, PANSS Positive subscale score is reduced by 90% or more. In some embodiments, after treatment, PANSS Positive subscale score is reduced by 80% or more. In some embodiments, after treatment, PANSS Positive subscale score is reduced by 70% or more. In some embodiments, after treatment, PANSS Positive subscale score is reduced by 60% or more. In some embodiments, after treatment, PANSS Positive subscale score is reduced by 50% or more. In some embodiments, after treatment, PANSS Positive subscale score is reduced by 40% or more. In some embodiments, after treatment, PANSS Positive subscale score is

reduced by 30% or more. In some embodiments, after treatment, PANSS Positive subscale score is reduced by 20% or more. In some embodiments, after treatment, PANSS Positive subscale score is reduced by 10% or more. In some embodiments, after treatment, PANSS Positive subscale score is reduced by 5% or more. In some embodiments, after treatment, PANSS Negative subscale score is reduced by 90% or more. In some embodiments, after treatment, PANSS Negative subscale score is reduced by 80% or more. In some embodiments, after treatment, PANSS Negative subscale score is reduced by 70% or more. In some embodiments, after treatment, PANSS Negative subscale score is reduced by 60% or more. In some embodiments, after treatment, PANSS Negative subscale score is reduced by 50% or more. In some embodiments, after treatment, PANSS Negative subscale score is reduced by 40% or more. In some embodiments, after treatment, PANSS Negative subscale score is reduced by 30% or more. In some embodiments, after treatment, PANSS Negative subscale score is reduced by 20% or more. In some embodiments, after treatment, PANSS Negative subscale score is reduced by 10% or more. In some embodiments, after treatment, PANSS Negative subscale score is reduced by 5% or more. In some embodiments, after treatment, BPRS total score is reduced by 90% or more. In some embodiments, after treatment, BPRS total score is reduced by 80% or more. In some embodiments, after treatment, BPRS total score is reduced by 70% or more. In some embodiments, after treatment, BPRS total score is reduced by 60% or more. In some embodiments, after treatment, BPRS total score is reduced by 50% or more. In some embodiments, after treatment, BPRS total score is reduced by 40% or more. In some embodiments, after treatment, BPRS total score is reduced by 30% or more. In some embodiments, after treatment, BPRS total score is reduced by 20% or more. In some embodiments, after treatment, BPRS total score is reduced by 10% or more. In some embodiments, after treatment, BPRS total score is reduced by 5% or more.

[0183] In some embodiments, clinical improvement for depression before and/or after treatment is evaluated using the Montgomery-Asberg Depression Rating Scale (MADRS). In some embodiments, after treatment, MADRS total score is reduced by 90% or more. In some embodiments, after treatment, MADRS total score is reduced by 80% or more. In some embodiments, after treatment, MADRS total score is reduced by 70% or more. In some embodiments, after treatment, MADRS total score is reduced by 60% or more. In some embodiments, after treatment, MADRS total score is reduced by 50% or more. In some embodiments, after treatment, MADRS total score is reduced by 40% or more. In some embodiments, after treatment, MADRS total score is reduced by 30% or more. In some embodiments, after treatment, MADRS total score is reduced by 20% or more. In some

embodiments, after treatment, MADRS total score is reduced by 10% or more. In some embodiments, after treatment, MADRS total score is reduced by 5% or more.

[0184] With respect to anti-NMDAR encephalitis, treatment includes, but is not limited to administering to the individual a therapeutic anti-NMDAR antibody or an anti-NMDAR binding fragment thereof that prevents binding of the pathologic anti-NMDAR autoantibody to an NMDA receptor of the individual, based upon detecting the presence of the pathologic anti-NMDAR antibody. In some embodiments, the therapeutic anti-NMDAR antibody comprises a one-armed anti-human NR1 antibody. In some embodiments, the therapeutic anti-NMDAR antibody reduces internalization of the NMDAR in the presence of the pathogenic anti-NMDAR antibody. In some embodiments, the therapeutic anti-NMDAR antibody reduces internalization of the NMDAR in the presence of the pathogenic anti-NMDAR antibody, wherein the pathogenic anti-NMDAR antibody comprises 102 Ab. In some embodiments, the therapeutic anti-NMDAR antibody reduces internalization of the NMDAR by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% in the presence of the pathogenic anti-NMDAR antibody, wherein the pathogenic anti-NMDAR antibody comprises 102 Ab. In some embodiments, the one-armed anti-human NR1 antibody comprises ART5803.

[0185] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 13, a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 14, and a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 15; and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 16, a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 17, and a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 18.

[0186] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 11.

[0187] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 11.

[0188] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 11.

[0189] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 25, at least 30, at least 35, at least 40, or at least 45 insertions, deletions, and/or substitutions relative to SEQ ID NO: 11.

[0190] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, at most 13, at most 14, at most 15, at most 16, at most 17, at most 18, at most 19, at most 20, at most 25, at most 30, at most 35, at most 40, or at most 45 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 11.

[0191] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, or 45 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 11.

[0192] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0193] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 12.

[0194] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 12.

[0195] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 12.

[0196] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at

least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 22 insertions, deletions, and/or substitutions relative to SEQ ID NO: 12.

[0197] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, at most 13, at most 14, at most 15, at most 16, at most 17, at most 18, at most 19, at most 20, or at most 22 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 12.

[0198] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 22 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 12.

[0199] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0200] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 23, a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 24, and a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 25; and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 26, a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence EDN, and a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 28.

[0201] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 21.

[0202] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 21.

[0203] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 21.

[0204] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 insertions, deletions, and/or substitutions relative to SEQ ID NO: 21.

[0205] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, or at most 13 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 21.

[0206] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 21.

[0207] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0208] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 22.

[0209] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 22.

[0210] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 22.

[0211] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, or at least 12 insertions, deletions, and/or substitutions relative to SEQ ID NO: 22.

[0212] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, or at most 12 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 22.

[0213] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 22.

[0214] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0215] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 33, a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 34, and a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 35; and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 36, a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 37, and a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 38.

[0216] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 31.

[0217] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 31.

[0218] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 31.

[0219] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 insertions, deletions, and/or substitutions relative to SEQ ID NO: 31.

[0220] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at

most 11, at most 12, or at most 13 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 31.

[0221] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 31.

[0222] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0223] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 32.

[0224] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 32.

[0225] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 32.

[0226] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, or at least 12 insertions, deletions, and/or substitutions relative to SEQ ID NO: 32.

[0227] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, or at most 12 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 32.

[0228] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 32.

[0229] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0230] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 43, a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 44, and a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 45; and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 46, a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 47, and a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 48.

[0231] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 41.

[0232] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 41.

[0233] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 41.

[0234] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 insertions, deletions, and/or substitutions relative to SEQ ID NO: 41.

[0235] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, or at most 13 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 41.

[0236] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 41.

[0237] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0238] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 42.

[0239] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 42.

[0240] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 42.

[0241] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, or at least 12 insertions, deletions, and/or substitutions relative to SEQ ID NO: 42.

[0242] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, or at most 12 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 42.

[0243] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 42.

[0244] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0245] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 53, a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 54, and a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 55; and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID

NO: 56, a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 57, and a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 58.

[0246] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 51.

[0247] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 51.

[0248] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 51.

[0249] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 insertions, deletions, and/or substitutions relative to SEQ ID NO: 51.

[0250] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, or at most 13 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 51.

[0251] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 51.

[0252] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0253] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 52.

[0254] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 52.

[0255] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 52.

[0256] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, or at least 12 insertions, deletions, and/or substitutions relative to SEQ ID NO: 52.

[0257] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, or at most 12 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 52.

[0258] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 52.

[0259] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0260] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 63, a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 64, and a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 65; and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 66, a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 67, and a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 68.

[0261] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 61.

[0262] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 61.

[0263] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 61.

[0264] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, or at least 13 insertions, deletions, and/or substitutions relative to SEQ ID NO: 61.

[0265] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, at most 12, or at most 13 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 61.

[0266] In some embodiments, the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 61.

[0267] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0268] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity or sequence similarity to SEQ ID NO: 62.

[0269] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 62.

[0270] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with one or more insertions, deletions, and/or substitutions relative to SEQ ID NO: 62.

[0271] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, or at least 12 insertions, deletions, and/or substitutions relative to SEQ ID NO: 62.

[0272] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence with at most 1, at most 2, at most 3, at most 4, at most 5, at most 6, at most 7, at most 8, at most 9, at most 10, at most 11, or at most 12 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 62.

[0273] In some embodiments, the therapeutic anti-NMDAR antibody comprises a light chain immunoglobulin variable region comprising an amino acid sequence comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 amino acid insertions, deletions, and/or substitutions relative to SEQ ID NO: 62.

[0274] The one or more insertions, deletions, and/or substitutions can be at the N-terminus, the C-terminus, within the amino acid sequence, or a combination thereof. The one or more insertions can be contiguous, non-contiguous, or a combination thereof.

[0275] In some embodiments, the method of detecting a pathologic anti-NMDAR autoantibody in a biological sample of an individual further comprises quantifying a level of the anti-NMDAR autoantibody in the biological sample.

[0276] In some embodiments, the level of the pathologic anti-NMDAR autoantibody in the biological sample of the individual is at a concentration of at most about 500 nM, at most about 400 ng/ml, at most about 300 ng/ml, at most about 200 ng/ml, at most about 100 ng/ml, at most about 90 ng/ml, at most about 80 ng/ml, at most about 70 ng/ml, at most about 60 ng/ml, at most about 50 ng/ml, at most about 40 ng/ml, at most about 30 ng/ml, at most about 20 ng/ml, at most about 10 ng/ml, at most about 5 ng/ml, at most about 2 ng/ml, or at most about 1 ng/ml or more.

[0277] In some embodiments, the level of the pathologic anti-NMDAR autoantibody in the biological sample of the individual is at a concentration of at least about 500 ng/ml, at least about 400 ng/ml, at least about 300 ng/ml, at least about 200 ng/ml, at least about 100 ng/ml, at least about 90 ng/ml, at least about 80 ng/ml, at least about 70 ng/ml, at least about 60 ng/ml, at least about 50 ng/ml, at least about 40 ng/ml, at least about 30 ng/ml, at least about 20 ng/ml, at least about 10 ng/ml, at least about 5 ng/ml, at least about 2 ng/ml, or at least about 1 ng/ml.

[0278] In some embodiments, the level of the pathologic anti-NMDAR autoantibody in the biological sample of the individual is at a concentration of about 500 ng/ml or less, about 400 ng/ml, about 300 ng/ml, about 200 ng/ml, about 100 ng/ml, about 90 ng/ml, about 80 ng/ml, about 70 ng/ml, about 60 ng/ml, about 50 ng/ml, about 40 ng/ml, about 30 ng/ml, about 20 ng/ml, about 10 ng/ml, about 5 ng/ml, about 2 ng/ml, or about 1 ng/ml.

[0279] In some embodiments, the level of the pathologic anti-NMDAR autoantibody in the biological sample of the individual is at a concentration ranging from 1 to 500 ng/ml, 2 to 500 ng/ml, 5 to 500 ng/ml, 10 to 500 ng/ml, 20 to 500 ng/ml, 30 to 500 ng/ml, 40 to 500 ng/ml, 50 to 500 ng/ml, 60 to 500 ng/ml, 70 to 500 ng/ml, 80 to 500 ng/ml, 90 to 500 ng/ml, 100 to 500

ng/ml, 200 to 500 ng/ml, 300 to 500 ng/ml, 400 to 500 ng/ml, 1 to 400 ng/ml, 2 to 400 ng/ml, 5 to 400 ng/ml, 10 to 400 ng/ml, 20 to 400 ng/ml, 30 to 400 ng/ml, 40 to 400 ng/ml, 50 to 400 ng/ml, 60 to 400 ng/ml, 70 to 400 ng/ml, 80 to 400 ng/ml, 90 to 400 ng/ml, 100 to 400 ng/ml, 200 to 400 ng/ml, 300 to 400 ng/ml, 1 to 300 ng/ml, 2 to 300 ng/ml, 5 to 300 ng/ml, 10 to 300 ng/ml, 20 to 300 ng/ml, 30 to 300 ng/ml, 40 to 300 ng/ml, 50 to 300 ng/ml, 60 to 300 ng/ml, 70 to 300 ng/ml, 80 to 300 ng/ml, 90 to 300 ng/ml, 100 to 300 ng/ml, 200 to 300 ng/ml, 1 to 200 ng/ml, 2 to 200 ng/ml, 5 to 200 ng/ml, 10 to 200 ng/ml, 20 to 200 ng/ml, 30 to 200 ng/ml, 40 to 200 ng/ml, 50 to 200 ng/ml, 60 to 200 ng/ml, 70 to 200 ng/ml, 80 to 200 ng/ml, 90 to 200 ng/ml, 100 to 200 ng/ml, 1 to 100 ng/ml, 2 to 100 ng/ml, 5 to 100 ng/ml, 10 to 100 ng/ml, 20 to 100 ng/ml, 30 to 100 ng/ml, 40 to 100 ng/ml, 50 to 100 ng/ml, 60 to 100 ng/ml, 70 to 100 ng/ml, 80 to 100 ng/ml, 90 to 100 ng/ml, 1 to 90 ng/ml, 2 to 90 ng/ml, 5 to 90 ng/ml, 10 to 90 ng/ml, 20 to 90 ng/ml, 30 to 90 ng/ml, 40 to 90 ng/ml, 50 to 90 ng/ml, 60 to 90 ng/ml, 70 to 90 ng/ml, 80 to 90 ng/ml, 1 to 80 ng/ml, 2 to 80 ng/ml, 5 to 80 ng/ml, 10 to 80 ng/ml, 20 to 80 ng/ml, 30 to 80 ng/ml, 40 to 80 ng/ml, 50 to 80 ng/ml, 60 to 80 ng/ml, 70 to 80 ng/ml, 1 to 70 ng/ml, 2 to 70 ng/ml, 5 to 70 ng/ml, 10 to 70 ng/ml, 20 to 70 ng/ml, 30 to 70 ng/ml, 40 to 70 ng/ml, 50 to 70 ng/ml, 60 to 70 ng/ml, 1 to 60 ng/ml, 2 to 60 ng/ml, 5 to 60 ng/ml, 10 to 60 ng/ml, 20 to 60 ng/ml, 30 to 60 ng/ml, 40 to 60 ng/ml, 50 to 60 ng/ml, 1 to 50 ng/ml, 2 to 50 ng/ml, 5 to 50 ng/ml, 10 to 50 ng/ml, 20 to 50 ng/ml, 30 to 50 ng/ml, 40 to 50 ng/ml, 1 to 40 ng/ml, 2 to 40 ng/ml, 5 to 40 ng/ml, 10 to 40 ng/ml, 20 to 40 ng/ml, 30 to 40 ng/ml, 1 to 30 ng/ml, 2 to 30 ng/ml, 5 to 30 ng/ml, 10 to 30 ng/ml, 20 to 30 ng/ml, 1 to 20 ng/ml, 2 to 20 ng/ml, 5 to 20 ng/ml, 10 to 20 ng/ml, 1 to 10 ng/ml, 2 to 10 ng/ml, 5 to 10 ng/ml, 1 to 5 ng/ml, 2 to 5 ng/ml, or 1 to 2 ng/ml.

[0280] In some embodiments, the method of detecting a pathologic anti-NMDAR autoantibody in a biological sample of an individual further comprises generating a report that indicates the presence of or the level of the anti-NMDAR antibody in the biological sample.

[0281] In some embodiments, the report comprises the presence of or level of anti-NMDAR autoantibodies, the diagnosis of the diseases associated with anti-NMDAR autoantibodies, or treatment recommendations for therapeutic agents. In some embodiments, the report comprises the presence of or the level of anti-NMDAR autoantibodies. In some embodiments, the report comprises the diagnosis of the diseases associated with anti-NMDAR autoantibodies disclosed herein. In some embodiments, the report comprises treatment recommendations for therapeutic agents such as ART5803. In some embodiments, the report is on physical media such as a paper, or stored and displayed on a computer, a phone, or a tablet. In some embodiments, the report is sent to a healthcare provider.

[0282] It is understood by those of skill in the art that not all individuals will respond equally or at all to a treatment that is administered, nevertheless these individuals are considered to be treated.

[0283] In certain embodiments, the antibodies can be administered to a subject in need thereof by any route suitable for the administration of antibody-containing pharmaceutical compositions, such as, for example, subcutaneous, intraperitoneal, intravenous, intramuscular, intratumoral, or intracerebral, etc. In certain embodiments, the antibodies are administered intravenously. In certain embodiments, the antibodies are administered subcutaneously. In certain embodiments, the antibodies are administered intratumoral. In certain embodiments, the antibodies are administered on a suitable dosage schedule, for example, weekly, twice weekly, monthly, twice monthly, once every two weeks, once every three weeks, or once a month etc. In certain embodiments, the antibodies are administered once every three weeks. The antibodies can be administered in any therapeutically effective amount. In certain embodiments, the therapeutically acceptable amount is ranging from 0.1 to 100 mg/kg, 0.1 to 90 mg/kg, 0.1 to 80 mg/kg, 0.1 to 70 mg/kg, 0.1 to 60 mg/kg, 0.1 to 50 mg/kg, 0.1 to 40 mg/kg, 0.1 to 30 mg/kg, 0.1 to 20 mg/kg, 0.1 to 10 mg/kg, 0.1 to 5 mg/kg, 0.1 to 1 mg/kg, 0.1 to 0.5 mg/kg, 0.5 to 100 mg/kg, 0.5 to 90 mg/kg, 0.5 to 80 mg/kg, 0.5 to 70 mg/kg, 0.5 to 60 mg/kg, 0.5 to 50 mg/kg, 0.5 to 40 mg/kg, 0.5 to 30 mg/kg, 0.5 to 20 mg/kg, 0.5 to 10 mg/kg, 0.5 to 5 mg/kg, 0.5 to 1 mg/kg, 1 to 100 mg/kg, 1 to 90 mg/kg, 1 to 80 mg/kg, 1 to 70 mg/kg, 1 to 60 mg/kg, 1 to 50 mg/kg, 1 to 40 mg/kg, 1 to 30 mg/kg, 1 to 20 mg/kg, 1 to 10 mg/kg, 1 to 5 mg/kg, 5 to 100 mg/kg, 5 to 90 mg/kg, 5 to 80 mg/kg, 5 to 70 mg/kg, 5 to 60 mg/kg, 5 to 50 mg/kg, 5 to 40 mg/kg, 5 to 30 mg/kg, 5 to 20 mg/kg, 5 to 10 mg/kg, 10 to 100 mg/kg, 10 to 90 mg/kg, 10 to 80 mg/kg, 10 to 70 mg/kg, 10 to 60 mg/kg, 10 to 50 mg/kg, 10 to 40 mg/kg, 10 to 30 mg/kg, 10 to 20 mg/kg, 20 to 100 mg/kg, 20 to 90 mg/kg, 20 to 80 mg/kg, 20 to 70 mg/kg, 20 to 60 mg/kg, 20 to 50 mg/kg, 20 to 40 mg/kg, 20 to 30 mg/kg, 30 to 100 mg/kg, 30 to 90 mg/kg, 30 to 80 mg/kg, 30 to 70 mg/kg, 30 to 60 mg/kg, 30 to 50 mg/kg, 30 to 40 mg/kg, 40 to 100 mg/kg, 40 to 90 mg/kg, 40 to 80 mg/kg, 40 to 70 mg/kg, 40 to 60 mg/kg, 40 to 50 mg/kg, 50 to 100 mg/kg, 50 to 90 mg/kg, 50 to 80 mg/kg, 50 to 70 mg/kg, 50 to 60 mg/kg, 60 to 100 mg/kg, 60 to 90 mg/kg, 60 to 80 mg/kg, 60 to 70 mg/kg, 70 to 100 mg/kg, 70 to 90 mg/kg, 70 to 80 mg/kg, 80 to 100 mg/kg, 80 to 90 mg/kg, or 90 to 100 mg/kg. In some embodiments, the therapeutically acceptable amount is from 1 mg/kg to 100 mg/kg. In some embodiments, the therapeutically acceptable amount is from 2 mg/kg to 50 mg/kg. In some embodiments, the therapeutically acceptable amount is from 2 mg/kg to 30 mg/kg. In some embodiments, the therapeutically acceptable amount is from 2 mg/kg to 20 mg/kg. Therapeutically effective amounts include amounts sufficient to ameliorate one or more symptoms associated with the disease or affliction to be treated.

Pharmaceutically acceptable excipients, carriers, and diluents

[0284] In certain embodiments the anti-NMDAR antibodies of the current disclosure are included in a pharmaceutical composition comprising one or more pharmaceutically acceptable excipients, carriers, and diluents. Pharmaceutically acceptable excipients, carriers and diluents can be included to increase shelf-life, stability, or the administrability of the antibody. Such compounds include salts, pH buffers, detergents, anti-coagulants, and preservatives. In certain embodiments, the antibodies of the current disclosure are administered suspended in a sterile solution. In certain embodiments, the solution comprises about 0.9% NaCl. In certain embodiments, the solution comprises about 5.0% dextrose. In certain embodiments, the solution further comprises one or more of: buffers, for example, acetate, citrate, histidine, succinate, phosphate, bicarbonate and hydroxymethylaminomethane (Tris); surfactants, for example, polysorbate 80 (Tween 80), polysorbate 20 (Tween 20), and poloxamer 188; polyol/disaccharide/polysaccharides, for example, glucose, dextrose, mannose, mannitol, sorbitol, sucrose, trehalose, and dextran 40; amino acid, for example, glycine or arginine; antioxidants, for example, ascorbic acid, methionine; or chelating agents, for example, EDTA or EGTA.

[0285] In certain embodiments, the antibodies of the current disclosure can be shipped/stored lyophilized and reconstituted before administration. In certain embodiments, lyophilized antibody formulations comprise a bulking agent such as, mannitol, sorbitol, sucrose, trehalose, dextran 40, or combinations thereof. The lyophilized formulation can be contained in a vial comprised of glass or other suitable non-reactive material. The antibodies when formulated, whether reconstituted or not, can be buffered at a certain pH, generally less than 7.0. In certain embodiments, the pH can be between 4.5 and 7.0, 4.5 and 6.5, 4.5 and 6.0, 4.5 and 5.5, 4.5 and 5.0, or 5.0 and 6.0.

[0286] Also described herein are kits comprising one or more of the antibodies described herein in a suitable container and one or more additional components selected from: instructions for use; a diluent, an excipient, a carrier, and a device for administration.

[0287] In certain embodiments, described herein is a method of preparing an anti-NMDAR receptor encephalitis treatment comprising admixing one or more pharmaceutically acceptable excipients, carriers, or diluents and an antibody of the current disclosure. In certain embodiments, described herein is a method of preparing an anti-NMDAR receptor encephalitis treatment for storage or shipping comprising lyophilizing one or more antibodies of the current disclosure.

EXAMPLES

[0288] The following illustrative examples are representative of embodiments of compositions and methods described herein and are not meant to be limiting in any way.

Example 1: Non-randomly coated NTD-NR1 on a solid support allows for strong detection of pathogenic antibody in an ELISA assay.

[0289] Previous studies have shown that the N-terminal domain (NTD) of NR1 subunit of NMDAR is the autoantibody binding target in anti-NMDAR encephalitis patients. The pathogenic anti-NMDAR NR1 autoantibody recognizes selective epitopes in the NTD of NR1 subunit, inducing cross-linking of NMDARs and their internalization, leading to hypo-NMDAR status. Previous work identified the epitope sequence in the NTD of NR1 subunit targeted by the pathogenic autoantibody 102 Ab. One-armed antibody ART5803 was generated to block the pathogenic autoantibody 102 Ab from binding to NMDAR subunit NR1. ART5803 binds to the same epitope as 102 Ab.

[0290] Since the pathogenic autoantibody binds to limited epitopes in the NTD of NMDAR NR1, the orientation of the NTD of NR1 affects the binding affinity of pathogenic autoantibody. To test whether the direction of the NTD of NR1 affects the binding affinity of pathogenic autoantibody, a 96 well nickel plate was coated with 200 ng/well of NTD-NR1-His-Avi, and binding to pathogenic monoclonal autoantibody 102 Ab (having the VH of SEQ ID NO: 79 and VL of SEQ ID NO: 80) and therapeutic antibody ART5803 were evaluated in an ELISA assay. Randomly coated NTD-NR1-His-Avi was used as a control. All the experiments were performed in assay buffer.

[0291] Specifically, for randomly coated NTD-NR1-His-Avi plates, maxisorp plate (ThermoFisher, #436110) was coated randomly with 8x His tagged NR1 ("8x His" disclosed as SEQ ID NO: 70) diluted in 1x TBS to 2ug/mL, added at 100uL per well, and incubated overnight at 4°C. Then the plate was washed 5 times with 200uL 1x TBST (Biotek EL 406) and all subsequent wash steps were performed identically. Undiluted Blocking One (BO; Nacalai Tesque, #03953-95) was added at 200uL per well and incubated for 1 hour at room temperature. All subsequent incubations were performed at room temperature. The plate was washed and antibodies serially diluted in 5% BO/1x TBS was added at 100uL per well and incubated for 2 hours. The plate was washed and 100uL of goat anti human IgG HRP conjugate (Bethyl, #A80-140P) at 1:15,000 in 5% BO/1x TBS was added to the plate. After the plate was washed, BM Chemiluminescence ELISA Substrate (Roche, #11582950001) was prepared according to the manufacturer's instruction and added to the plate at 100uL per well. After 10 minutes of incubation, chemiluminescence

measurements were read by PerkinElmer Multimode Plate Reader Victor X5. Data was analyzed with GraphPad Prism 9.

[0292] For non-randomly coated NTD-NR1-His-Avi plates, Pierce Nickel Coated Plate (ThermoFisher #15241) was prewashed with 200uL 1x TBST and non-randomly coated with 8x His tagged NR1 (“8x His” disclosed as SEQ ID NO: 70) diluted in 1x TBS to 2ug/mL, added at 100uL per well, and incubated overnight at 4°C. The plate was washed 5 times with 200uL 1x TBST (Biotek EL 406) and all subsequent wash steps were performed identically. Plate was washed and antibodies serially diluted in 5% Bocking One (BO; Nacalai Tesque, #03953-95)/1x TBS were added at 100uL per well and incubated for 2 hours. All subsequent incubations were also performed at room temperature. The plate was washed and 100uL of goat anti human IgG HRP conjugate (Bethyl, #A80-140P) diluted to 1:15,000 in 5% BO/1x TBS was added to the plate. After the plate was washed, BM Chemiluminescence ELISA Substrate (Roche, #11582950001) was prepared according to the manufacturer’s instruction and added to the plate at 100uL per well. After 10 minutes of incubation, chemiluminescence measurements were read by PerkinElmer Multimode Plate Reader Victor X5. Data was analyzed with GraphPad Prism 9.

[0293] The results of the EC₅₀ of ART5803 and 102 Ab in randomly and non-randomly coated NTD-NR1 are shown in Table 1. ART5803 showed strong signal in both the randomly and the non-randomly coated NTD-NR1 plate (**FIG. 2A** and **FIG. 2B**). 102 Ab exhibited much lower binding affinity compared with ART5803 in the randomly coated NTD-NR1 plate (**FIG. 2A**). However, the signal of 102 Ab was improved in the non-randomly coated NTD-NR1 plate and similar to the signal of ART5803 (**FIG. 2B**). This result suggests that the non-randomly coated NTD-NR1 plate increased the sensitivity of the ELISA detecting pathogenic autoantibody 102 Ab. Without wishing to be bound by any particular theory, the improved sensitivity can be due to the direction of the epitopes of NTD-NR1 favoring the stabilization of 102 Ab binding to the NTD-NR1 (**FIG. 1A** and **FIG. 1B**).

[0294] TABLE 1

Trial #	Random Coating EC ₅₀ [μg/mL]		Non-Random Coating EC ₅₀ [μg/mL]	
	ART5803	102 Ab	ART5803	102 Ab
1	0.062	1.70	0.013	0.038
2	0.058	1.83	0.017	0.037

[0295] Opentrons OT-2 automated liquid handler and Opentrons Protocol Designer (v7.0) were used for the following protocol except where noted. Before coating, Pierce Neutravidin Coated White 384-well Plate (ThermoFisher, Ref# 15401) was first blocked with 100 μ L per well of 3 % Pure BSA IgG-Free (Jackson ImmunoResearch, Ref# 001-000-162) in 1x TBS (20X TBS, ThermoFisher, Ref# 28358) and incubated for 1 hour at room temperature. The plate was then washed 3 times with 100 μ L 1x TBST (20X TBST, ThermoFisher, Ref# PI28360) using a plate washer (Biotek, Model# EL 406). The plate was coated with 50 μ L per well of 5 μ g/mL Biotinylated His-Avi tagged Human NR1 in 1x TBS. In non-antigen coated control wells, 50 μ L per well of 1x TBS was added then centrifuged for 2 mins at 1,200 RPM (Eppendorf, Model# 5910RI) and incubated overnight at 4 °C. The plate was then washed 5 times with 100 μ L 1x TBST using a plate washer. All subsequent wash steps were performed identically. The plate was blocked again with 100 μ L per well of 3% Pure BSA in 1x TBS and incubated for 1 hour at room temperature. Patient derived anti-NMDA receptor autoantibodies (102Ab, 218Ab, 168Ab, 124Ab) were first diluted manually in PBS, pH 7.4 (ThermoFisher, Ref# 10010-023) to 1.0 mg/mL and subsequently serially diluted 3 folds in 50% Blocking One (BO; Nacalai Tesque, Ref# 03953-95) /1x TBS/ 10% healthy human pooled serum (Cosmo Bio, Cat# KOJ-12181201C, Lot# 20090730) or CSF (BIO IVT, Cat# 12102021-CSF-20-2001, Lot# 102021-CSF-20) in a 96-well Deepwell PP Nunc Plate (Fisher Scientific, Cat# 260251) by OT-2. After blocking for 1 hour, the plate was washed, and serially diluted autoantibodies were added at 50 μ L per well to designated wells. Then, the plate was centrifuged for 2 mins at 1,200 RPM and incubated for 2 hours at room temperature. All subsequent incubations were also performed at room temperature. After 2 hours incubation, the plate was washed and 50 μ L of 1:15,000 diluted goat anti-human IgG HRP conjugate (Bethyl, #A80-140P) in 10% BO/1x TBS. The plate was centrifuged for 2 mins at 1200 RPM and incubated for another 2 hours. After incubation, plate was washed and BM Chemiluminescence ELISA Substrate (POD, Roche, #11582950001) was prepared according to the manufacturer's instruction then added to the plate at 50 μ L per well. After 10 mins incubation, chemiluminescence measurements were read by PerkinElmer Multimode Plate Reader Victor X5 and data was analyzed with GraphPad Prism (v10.0.2).

Example 2A: Non-randomly coated NTD-NR1 on a solid support allows for strong detection of weak affinity pathogenic antibody in an ELISA assay.

[0296] Since the binding affinity of 102 Ab was improved in a non-randomly coated NTD-NR1 plate, three weaker affinity pathogenic monoclonal autoantibodies were tested in the non-randomly coated NTD-NR1 ELISA system, with the randomly coated NTD-NR1 used as a control. The assay was performed essentially as described in Example 1. All three pathogenic monoclonal autoantibodies showed almost non-detectable signal when using the randomly coated NTD-NR1

plate (**FIG. 3A**). 218 Ab, 168 Ab, and 124 Ab showed improved signal in the non-randomly coated NTD-NR1 plate (**FIG. 3B**). This result suggests the non-randomly coated NTD-NR1 ELISA system can improve the detection of certain weak affinity NMDAR autoantibodies as compared to the randomly coated NTD-NR1 ELISA system.

[0297] Similar non-randomly coated NTD-NR1 ELISA system were prepared using a Pierce Neutravidin Coated White 384-well Plate (ThermoFisher, Ref# 15401) with Biotinylated His-Avi tagged Human NR1. Like the nickel substrate ELISA system, the Pierce Neutravidin Coated detected all tested pathogenic monoclonal autoantibodies (**FIG. 6A** and **FIG. 6B**). Indeed, as shown in **FIG. 6A** and **FIG. 6B**, these results were obtainable using different biological samples, including serum and CSF, respectively. In the avidin coated system, the avidin coated biotinylated NTD-NR1 ELISA system showed very strong detection for all tested pathogenic monoclonal autoantibodies and good compatibility with high concentrations of healthy human pooled serum and CSF (up to 20% tested, data not shown).

[0298] Various autoantibodies (e.g., IgG/IgA/IgM) were also evaluated in patients' sera by the non-randomly coated NTD-NR1 ELISA system (not shown). Previous data showed that the randomly coated NTD-NR1 ELISA system can only detected low signal of IgG. In some embodiments, the non-randomly coated NTD-NR1 ELISA system can detect IgG/IgA/IgM in patients with weaker affinity NMDAR autoantibodies.

[0299] Using a Pierce Neutravidin Coated White 384-well Plate (ThermoFisher, Ref# 15401) with Biotinylated His-Avi tagged Human NR1 similar to as described in Example 1. The Pierce Neutravidin Coated detected all tested IgG, IgA, and IgM (**FIG. 8A** and **FIG. 8B**) (102 Ab). Indeed, as shown in **FIG. 8A** and **FIG. 8B**, these results were obtainable using different biological samples, including serum and CSF, respectively.

Example 2B: 102 IgG/A/M NMDAR Internalization assay

[0300] HEK293 cells stably transfected with tetracycline-inducible expression of human NMDA receptor (GluN1/GluN2B) were purchased from Charles River Discovery (Cleveland, OH, USA). T-REx-293 cells were purchased from Invitrogen (R71007) and prepared in parallel with the same treatments as NMDA receptor expressing HEK as a negative control. Cells were induced by 16-24hr incubation in Induction Medium (1.5×10^5 cells/100 μ L) consisting of Neurobasal Medium (Life Technologies Corporation, Carlsbad, CA, USA) with 10% dialyzed FBS, 50 U/mL penicillin-streptomycin, 2.0 μ g/mL tetracycline, and 0.2 mM memantine in collagen coated culture dishes. Then cells were harvested and cultured in a 96 well plate with the following antibodies for assessment of internalization activity. 102 IgG and 102 IgA monomer antibodies were 3 folds serially diluted at 0.0003-10 μ g/mL in induction medium, whereas 102 IgA dimer at 0.001-30 μ g/mL and 102 IgM at 0.003-100 μ g/mL. Antibodies were added to cells at 100 μ L/well and

incubated at 37 °C, 5% CO₂ for 16 hrs-24 hrs. From this point, all steps were kept on ice and washes were performed twice with FACS buffer 100 µL/well with subsequent centrifugation at 1200 rpm, 5min, 4°C. Cells were harvested into a 96 well round bottom plate, centrifuged, and media was discarded. Human Fc receptor binding inhibitor (1:50; Invitrogen, 14-0161-73) and Live/Dead fixable violet cell stain (1:666; Invitrogen, L34955) were added 100 µL/well for 15 min then centrifuged and supernatant was discarded. Cells were stained with 5 µg/ml of anti-NMDAR antibody 502Ab for 30 min. After a wash, cells were stained with APC conjugated goat anti-human IgG (1:100; Jackson ImmunoResearch Inc, West Grove, PA, USA) for 30 min, followed by a wash, and resuspension in 100 µL/well 4% PFA in PBS. The APC signal detection was performed by using Novocyt 2060 and NovoExpress v1.5.0. (Agilent Technologies, Santa Clara, CA). FlowJo v10.7.2 (BD Biosciences, Franklin lakes, NJ, USA) was used for the analysis of flow cytometry data. The data was represented as the mean of two internal replicates. Expression levels of NMDA receptors on the cell surface were calculated after normalization to the mean fluorescence intensity (MFI) of 502Ab staining as 100% surface expression and the MFI of isotype control antibody staining as 0% surface expression. Data was graphed in GraphPad Prism v10.0.2 (GraphPad Software, San Diego, CA, USA).

[0301] IgG, IgA, and IgM (102 Ab) all display pathogenicity, as they induce significant internalization of NMDAR (NR1) in a cell-based assay (**FIG. 7A**).

Example 2C: ART5803 blocks NMDAR internalization induced by 102 IgG/A/M

[0302] Using the NMDAR internalization assay method similar to as described in Example 2B, the following combinations of serially diluted ART5803 (final concentrations) were co-incubated with either 102 IgG, IgA dimer or IgM (final concentrations) with cells overnight at 37 °C, 5% CO₂ for 16-24 hours: 102 IgG at 10ug/mL with ART5803 3 folds serially diluted from 10-0.001 ug/mL. 102 IgA dimer at 3 ug/mL and co-incubated with ART5803 3 folds serially diluted from 10-0.001 ug/mL. 102 IgM at 3ug/mL and co-incubated with ART5803 3 folds serially diluted from 100-0.01 ug/mL. ART503 blocks NMDAR (NR1) internalization induced by IgG, IgA, and IgM (102 Ab) in a cell-based assay (**FIG. 7B**, **FIG. 7C**, and **FIG. 7D**).

Example 3: ART5803-Fab displaces bound NMDAR autoantibody from NTD-NR1.

[0303] If NMDAR autoantibody binds to the same epitope as ART5803, since ART5803 exhibited stronger affinity to NTD-NR1, it is possible that the binding of NMDAR autoantibody to the NTD-NR1 can be displaced by ART5803. An ART5803-Fab was generated and used to test whether the NMDAR autoantibodies can be displaced by ART5803-Fab in the non-randomly coated NTD-NR1 ELISA system (**FIG. 4**).

[0304] Specifically, Pierce Nickel Coated Plate (ThermoFisher #15241) was prewashed with 200uL 1x TBST and non-randomly coated with 8x His tagged NR1 ("8x His" disclosed as SEQ

ID NO: 70) diluted in 1x TBS to 2ug/mL, added at 100uL per well, and incubated overnight at 4 °C. The plate was washed 5 times with 200uL 1x TBST (Biotek EL 406) and all subsequent wash steps were performed identically. Serially diluted ART5803-Fab in 5% Blocking One (BO; Nacalai Tesque, #03953-95)/1x TBS was added to the plate at 50uL per well and incubated for 2 hours at room temperature. All subsequent incubation steps were also performed at room temperature. Based on previous assessment of the pathogenic monoclonal autoantibodies binding saturation dose on non-randomized coated NR1 ELISA, pathogenic antibodies were added to the plate at 50uL/well and incubated for 2 hours (final concentration 102 Ab at 0.12ug/mL, 124 Ab at 300ug/mL, 168 Ab at 33.33ug/mL, 3.7 ug/mL at 218 Ab ug/mL diluted in 5% BO/1x TBS). Plate was washed and 100uL of goat anti human IgG HRP conjugate (Bethyl, #A80-140P) at 1:15,000 diluted in 5% BO/1x TBS was added to the plate. After the plate was washed, BM Chemiluminescence ELISA Substrate (Roche, #11582950001) was prepared according to the manufacturer's instruction and added to the plate at 100uL per well. After 10 minutes of incubation, chemiluminescence measurements were read by PerkinElmer Multimode Plate Reader Victor X5. Data was transformed and normalized in GraphPad Prism 9 to assess percentage inhibition of pathogenic antibody binding by ART5803-Fab.

[0305] The binding of all four pathogenic monoclonal autoantibodies (102 Ab, 218 Ab, 168 Ab, and 124 Ab) to the NTD-NR1 was completely displaced at higher concentrations of the ART5803-Fab (**FIG. 5**), demonstrating that the ART5803-Fab competes for binding with the pathogenic monoclonal antibodies to NTD-NR1. This method can provide information regarding the autoantibody epitope binding specificity, pathogenicity, and whether patients with the autoantibody will be responsive to the ART5803 treatment.

[0306] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention.

[0307] All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

Sequence listings provided herein		
Name	SEQ ID NO:	Sequence

NTD-NR1	1	MSTMRLTLALLFSCSVARAACDPKIVNIGAVLSTRKHEQMREAV NQANKRHGSWKIQLNATSVTHKPNAIQMALSVCEDLISSQVYAILV SHPPTPNDFHTPTPVSYTAGFYRIPVLGLTTRMSIYSDKSIHLSFL RTVPPYSHQSSVWFEMMRVYSWNHIIILLVSDDHGAAQKRLETLL EERESKAQKVLQFDPGKNTALLMEAKELEARVILSASEDDAAT VYRAAAMLNMTGSGYVWLVGEREISGNALRYAPDGLGLQLINGKN ESAHISDAVGVAQAVHELLEKENITDPPRGCVGNTNIWKTGPLFK RVLMSKYADGVTGRVEFNEDGDRKFANYSIMNLQNRKLVQVGIYN GTHVIPNDRKIIWPGGETEKPRGYQ
NTD-NR1	2	HPPTPNDFHTPTPVSYTAGFYRIPVLGLTTRMSIYSDKSIHLSFLR TVPPYSHQSSVWFEMMRVYSWNHIIILLVSDDHGAAQKRLETLL ERESKAQKVLQFDPGKNTALLMEAKELEARVILSASEDDAATV YRAAAMLNMTGSGYVWLVGEREISGNALRYAPDGLGLQLINGKNE SAHISDAVGVAQAVHELLEKENITDPPRGCVGNTNIWKTGPLFKR VLMSSKYADGVTGRVEFNEDGDRKFANYSIMNLQNRKLVQVGIYNG THVIPNDRKIIWPGGETEKPRGYQ
NTD-NR1	3	YSHQSSVWFEMMRVYSWNHIIILLVSDDHGAAQKRLETLLERES KAQKVLQFDPGKNTALLMEAKELEARVILSASEDDAATVYRAA AMLNMTGSGYVWLVGEREISGNALRYAPDGLGLQLINGKNESAHIS DAVGVAQAVHELLEKENITDPPRGCVGNTNIWKTGPLFKRVLMS SKYADGVTGRVEFNEDGDRKFANYSIMNLQNRKLVQVGIYNGTHVI PNDRKIIWPGGETEKPRGYQ
NTD-NR1	4	VLQFDPGKNTALLMEAKELEARVILSASEDDAATVYRAAAMLN MTGSGYVWLVGEREISGNALRYAPDGLGLQLINGKNESAHISDAV GVVAQAVHELLEKENITDPPRGCVGNTNIWKTGPLFKRVLMSKYA DGVTGRVEFNEDGDRKFANYSIMNLQNRKLVQVGIYNGTHVIPNDR KIIWPGGETEKPRGYQ
NTD-NR1	5	NALRYAPDGLGLQLINGKNESAHISDAVGVAQAVHELLEKENIT DPPRGCVGNTNIWKTGPLFKRVLMSKYADGVTGRVEFNEDGDRKF ANYSIMNLQNRKLVQVGIYNGTHVIPNDRKIIWPGGET
NR1	6	MSTMRLTLALLFSCSVARAACDPKIVNIGAVLSTRKHEQMREAV NQANKRHGSWKIQLNATSVTHKPNAIQMALSVCEDLISSQVYAILV SHPPTPNDFHTPTPVSYTAGFYRIPVLGLTTRMSIYSDKSIHLSFL RTVPPYSHQSSVWFEMMRVYSWNHIIILLVSDDHGAAQKRLETLL EERESKAQKVLQFDPGKNTALLMEAKELEARVILSASEDDAAT VYRAAAMLNMTGSGYVWLVGEREISGNALRYAPDGLGLQLINGKN ESAHISDAVGVAQAVHELLEKENITDPPRGCVGNTNIWKTGPLFK RVLMSKYADGVTGRVEFNEDGDRKFANYSIMNLQNRKLVQVGIYN GTHVIPNDRKIIWPGGETEKPRGYQMSTRLKIVTIHQEPFVYVKPT LSDGTCKEEFTVNGDPVKKVICTGPNDTSPGSPRHTVPQCCYGFCI DLLIKARTMNFTYEVHLVADGKFGTQERVNNSNKKEWNGMMGELL SGQADMIVAPLTINNERAQYIEFSKPFKYQGLTILVKEIIPRSTLD SFMQPFQSTLWLLVGLSVHVAVMLYLLDRFSPFGRFKVNSEEEEE DALTLSSAMWFSWGVLLNSGIGEGAPRSFSARILGMVWAGFAMIIV ASYTANLAAFLVLDREPERITGINDPRLRNPSDKFIYATVKQSSVD IYFRRQVELSTMYRHMEKHNYESAAEAIQAVRDKNLHAFIWDASAVL EFEASQKCDLVTTGELFFRSGFGIGMRKDSFWKQNVSLSILKSHEN GFMEDLDKTWVRYQECDSRSNAPATLTFENMAGVFMVLVAGGIVAGI FLIFIEIAYKRHKDARRKQMQLAFAAVNVWRKNLQDRKSGRAEPDP KKKATFRAITSTLASSFKRRRSSKDTSTGGGRGALQNKQDVTLP AIEREEGQLQLCSRHRES

ART 5803_VH (ART 5803)	11	EVQLVESGGGLVQPGGSLRLSCKASGYAYTSYWMNWVRQAPGKGLV WVGRIDPYDSETHYNQKFKDRFTLSVDKAKSTTYLQMNSLRAEDTA VYYCATLITTLRGEGAMEYWGQGTLVTVSS
ART 5803_VL	12	DLQMTQSPSSLSASVGDRTITCKASQDVNTAVAWYQQKPGKAPKL LIYWASTRHTGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHY STPFTFGQGTKVEIKR
ART 5803_HCDR1	13	SYWMN
ART 5803_HCDR2	14	RIDPYDSETHYNQKFKD
ART 5803_HCDR3	15	LITTLRGEGAMEY
ART 5803_LCDR1	16	KASQDVNTAVA
ART 5803_LCDR2	17	WASTRHT
ART 5803_LCDR3	18	QQHYSTPFT
P_Fc LALA_W (Fc)	19	CPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLWCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSK LTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGK
Clone 1_VH	21	QVQLQESGPGLVKPSGTLSTLCAVSGGSISSSNWWSWVRQPPGKGL EWIGEIIYHSGNTNYPNPSLKSRTVSVVDKSKNQFSLKLTSVTAADTA VYYCARDVSGGVNWFDPPWGQGTLVTVSS
Clone 1_VL	22	NFMLTQPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRPGSAPT TVIYEDNQRPSPGVDPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQ SYDSSTVVFGGGTKLTVL
Clone 1_HCDR1 (26 to 34)	23	GGSISSSNW
Clone 1_HCDR2 (52 to 58)	24	IYHSGNT
Clone 1_HCDR3 (97 to 109)	25	ARDVSGGVNWFDPP
Clone 1_LCDR1 (26 to 33)	26	SGSIASNY
Clone 1_LCDR2 (51 to 53)		EDN
Clone 1_LCDR3 (92 to 100)	28	QSYDSSTVV
Clone2_VH	31	EVQLVQSGAEVKKPGESLKISCKGSGYTYTSYWMNWVRQMPGKGLE WMGRIDPYDSETHYDQKFKDQVTLSDKSI STAYLQWSSLKASDTA MYCAGGITITILGGYFDYWGQGTLVTVSS

Clone2_VL	32	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAPKL LIYYTSRLHSGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQGN TLPPYTFGQGTKVEIKR
Clone 2_HCDR1 (31 to 35)	33	SYWMN
Clone 2_HCDR2 (50 to 66)	34	RIDPYDSETHYDQKFKD
Clone 2_HCDR3 (99 to 110)	35	GITTILGGYFDY
Clone 2_LCDR1 (24 to 34)	36	RASQDISNYLN
Clone 2_LCDR2 (50 to 56)	37	YTSRLHS
Clone 2_LCDR3 (89 to 98)	38	QQGNTLPPYT
Clone3_VH	41	EVQLVESGGGLVQPGGSLRLSCKASGYAYTSYWMNWVRQAPGKGLV WVGRIDPYDSETHYNQKFKDRFTLSVDKAKSTTYLQMNSLRAEDTA VYYCATLITTLRGEGAMEYWGQGTLLTVSS
Clone3_VL	42	DLQMTQSPSSLSASVGDRVTITCKASQDVNTAVAWYQQKPGKAPKL LIYWASTRHTGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHY STPFTFGQGTKVEIKR
Clone 3_HCDR1 (31 to 35)	43	SYWMN
Clone 3_HCDR2 (50 to 66)	44	RIDPYDSETHYNQKFKD
Clone 3_HCDR3 (99 to 111)	45	LITTLRGEGAMEY
Clone 3_LCDR1 (24 to 34)	46	KASQDVNTAVA
Clone 3_LCDR2 (50 to 56)	47	WASTRHT
Clone 3_LCDR3 (89 to 97)	48	QQHYSTPFT
Clone4_VH	51	QVQLQESGPGLVKPSSETLSLTCSVTGYSITSDYYWHWIRQPPGKGL EWIAYIRYDGRNDYNPSLKNRVTISRDTSKNQFSLKLSSVTAADTA VYYCAREDYGSSSFYWGQGTLLTVSS
Clone4_VL	52	DIQMTQSPSSLSASVGDRVTITCRASENIYSNLAWYQQKPGKAPKL LVYAATNLADGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQHF DSPPTFGQGTKVEIKR

Clone 4_HCDR1 (31 to 36)	53	SDYYWH
Clone 4_HCDR2 (51 to 66)	54	YIRYDGRNDYNPSLKN
Clone 4_HCDR3 (99 to 108)	55	EDYGSSSFY
Clone 4_LCDR1 (24 to 34)	56	RASENIYSNLA
Clone 4_LCDR2 (50 to 56)	57	AATNLAD
Clone 4_LCDR3 (89 to 97)	58	QHFWDSPPT
Clone5_VH	61	QVQLQESGPGLVKPSQTLSTCSVTGYSITSDYYWHWIRQPPGKGL EWIAYIRYDGRNDSNPSLKNRVTISRDTSKNQFSLKLSSVTAADTA VYYCAREDYASSSFYWGQGTLLTVSS
Clone5_VL	62	DIQMTQSPSSLSASVGDRTITCRPSENIYSNLAWYQQKPGKAPKL LVYAATNLADGVPSRFSGSGSGTDYTLTISSLQPEDATYYCQHFWD DSPPTFGQGTKLEIKR
Clone 5_HCDR1 (31 to 36)	63	SDYYWH
Clone 5_HCDR2 (51 to 66)	64	YIRYDGRNDSNPSLKN
Clone 5_HCDR3 (99 to 108)	65	EDYASSSFY
Clone 5_LCDR1 (24 to 34)	66	RSENIYSNLA
Clone 5_LCDR2 (50 to 56)	67	AATNLAD
Clone 5_LCDR3 (89 to 97)	68	QHFWDSPPT
His	70	HHHHHHHH
c-Myc	71	EQKLISEEDL
HA	72	YPYDVPDYA
V5	73	GKPIPNPLLGLDST
GST	74	MSPILGYWKIKGLVQPTRLLLEYLEEKYEEHLYERDEGDKWRNKKF ELGLEFPNLPYYIDGDVKLTQSMATIRYIADKHNMGLGGCPKERAET SMLEGAVLDIRYGVSRVIAYSKDFETLKVDVFLSKLPEMLKMFEDRLC HKTYLNGDHVTHPDEMLYDALDVVLYMDPMCLDAFPKLVCFKKRIE AIPQIDKYLKSSKYIAWPLQGWQATFGGGDHPPKSD

MBP	75	MKIEEGKLV I WINGDKGYNG LAEVGKKFEK DTGIKVTVEH PDKLEEKFPQ VAATGDGPDI IFWAHDRFGG YAQSGLLAEI TPDKAFQDKL YPFTWDAVRY NGKLIAYPIAVEALSLIYNK DLLPNPPKTW EEIPALDKEL KAKGKSALMF NLQEPYFTWP LIAADGGYAF KYENGKYDIK DVGVDNAGAK AGLTFLVDLI KNKHMNADTD YSIAEAAFNK GETAMTINGP WAWSNIDTSK VNYGVTVLPT FKGQPSKPFV GVLSAGINAA SPNKELAKEF LENYLLTDEG LEAVNKDKPL GAVALKSYEE ELAKDPRIAA TMENAQKGEI MPNIPQMSAF WYAVRTAVIN AASGRQTVDE ALKDAQTNSS SNNNNNNNN NLGIEGR
CBP	76	KRRWKKNFIAVSAANRFKKISSSGAL
CBD	77	MGPQLATVSL LLLTFFSNSI QYPHSPAATE CPAYFNGNIA GNACGREYSI CVNGVRQAAT CSDDSVFYED ECVPVDESPE CRVDENTEED DTPYAEFDCT SKQDGIYSIG CSNQFISCVA GGAYMAKCPD SLVFNERQD CRESCDEVKQ DTTTAPQVYE DGEEGYGEAS GEIAGDYERQ PSNEQPDSID FDCNGLEDGN YADGCNDVFY SCSNNMVFQR YCPPGTVFNI NQQSCDFQCT TDDPTTTVSY STSTITTPQE DDSEYSSTTS ADVISTTTTP SIDAIETTTT GFDAVTTTTT TQTPFVCQEG QVNSFGMCSS RFNRCQNNVS RSKQCPVNTL FESSLVMCVF DLPQCQPITV PAAPAYNSYG PPSDTIVSPF DENVRCLKPKF DRRRKYHHGK PSYGPVNGNS YLENPFFIPR HRGGSHRDHR RYGYGPAIDS PFSTAFRGRA ALSDQFKDYR RARMGKIQGD ARKVDGNKRF LIDDEFEGPN AKFVESNIEQ VFPKNRHSKK QLGPHEDPDG YDDEKTFDAK DLFGATRRKR SAYYGTEQSV YGQQSAQISA RQAQVNKDCQ QYTTPTFLTF GDCFDQFIFC SGNGINRMAA CPIGETFDKT LRSCSETCGV STTIVAVTIG TQTSDDL SAP SEYIENDGVT TQSTWNDQPS TTQAPNSYES YTTQYSSNDV PSTSAAPIGD RCLDASGLF SLGCSQKYIQ CSNGAAIVRR CGESLYFNEA TQECTYRDEV PECGSQGSTS SPVITTPGQD QSSNYYGIPS DDVPSTTQTP VGDRCAVAS GLFDLGCSQK YIQCSDSAAS VRECEGSLYF DERSQSCRFR DEVFKCQTAD VSSSSTVPYL DFTTTPASPS EDEPTTYEPS VAPYIPSVTV NPVDTCTSL S DGTHGTGCSS FYFVCSHGRL ISSGNCQLGE GYDPSVQGCR TFSEIPARAC DEQEVTTDAG LVQLMPYKTL EEVLTTTEAA TTVANDGPTD TYITGSTKYS TTDSGEYTIP YGETTTSTRS YDRADNSED EEEDDVEHDQ KCTVGSRTPV GFCVRTYLEC TDAGNVEKLC RIGKLFDSHS NRCVPRIGCG KEAIRDAIKD MIATTPAPAQ PKQFEGRAH VDGEAVFSIG VCSSKYL RCS YGASKLQQCS EDRVFSNDKL ECIVRESVSA CTVPKNPSIK KYTTSNDQSA FCDGKEDGLY RNERDCSAIL QCFGGELFEH PSCQSSLAFN QLTGKCDYPQ KVSCENHGQ TNGECSEHGS FIADANNCEV FYRCVWGRKV VMTCPSGTVF NPLLSVCDWP SAVPSCSGQA SDSNSSYGSS TYNDDKSGY
Avi	78	GLNDIFEAQKIEWHE
102 ab VH	79	QVQLQESGPGLVKPSGTLSTCAVSGGSISSSNWWSWVRQPPGKGL EWIGEIIYHSGNTNYPNPSLKSRTVSVDKSKNQFSKLKTSVTAADTA VYYCARDVSGGVNWFDPWGQGLTVTVSS
102 ab VL	80	NFMLTQPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRPGSAPT TVIYEDNQRPSPGVPDRFSGSIDSSNSASLTISGLKTEDEADYYCQ SYDSSTVVFGGGTKLTVL

Mouse Fc (mFc)	81	LEVLFQGPSPPLKECPPCAAPDLLGGPSVFI FPPKIKDVLMI SLS PMVTCVVVDVSEDDPDVQISW FVNNVEVHTAQTQTHREDYNSTLRV VSALPIQH QDWMMSGKEFKCKVNNRALPSPIEKTISKPRGPVRAPQV YVLPPPAEEMTKKEFSLTCMITGFLPAEIAVDWTSNGRTEQNYKNT ATVLDS DGSYFMYSKLRVQKSTWERGSLFACSVVHEGLHNHLTTKT ISRSLGK
NR1-mFc	82	RAACDPKIVNIGAVLSTRKHEQMFREAVNQANKRHGSWKIQLNATS VTHKPNAIQMALSVCEDLISSQVYAILVSHPTPNDFHTPTPVSYT AGFYRIPVLGLTTRMSIYSDKSIHLSFLRTVPPYSHQSSVWFEMMR VYSWNHII LLVSDDHEGRAAQKRLETLL EERESKA EKVLQFDPGK NVTALLMEAKELEARV I ILSASEDDAATVYRAAAMLNMTGSGYVWL VGEREISGNALRYAPDGILGLQLINGKNESAHI SDAVGVAQAVHE LLEKENITDPPRGCVGNTNIWKTGPLFKRVLMS SKYADGVTGRVEF NEDGDRKFANYSIMNLQNRKLVQVGIYNGTHVIPNDRKI IWPGET EKPRGYQTGGSLEVLFQGPSPPLKECPPCAAPDLLGGPSVFI FPP KIKDVLMI SLSPMVTCVVVDVSEDDPDVQISW FVNNVEVHTAQTQ HREDYNSTLRVVSALPIQH QDWMMSGKEFKCKVNNRALPSPIEKTIS KPRGPVRAPQVYVLPPPAEEMTKKEFSLTCMITGFLPAEIAVDWTS NGRTEQNYKNTATVLDS DGSYFMYSKLRVQKSTWERGSLFACSVVH EGLHNHLTTKTISRSLGK
NTD-NR1	83	RAACDPKIVNIGAVLSTRKHEQMFREAVNQANKRHGSWKIQLNATS VTHKPNAIQMALSVCEDLISSQVYAILVSHPTPNDFHTPTPVSYT AGFYRIPVLGLTTRMSIYSDKSIHLSFLRTVPPYSHQSSVWFEMMR VYSWNHII LLVSDDHEGRAAQKRLETLL EERESKA EKVLQFDPGK NVTALLMEAKELEARV I ILSASEDDAATVYRAAAMLNMTGSGYVWL VGEREISGNALRYAPDGILGLQLINGKNESAHI SDAVGVAQAVHE LLEKENITDPPRGCVGNTNIWKTGPLFKRVLMS SKYADGVTGRVEF NEDGDRKFANYSIMNLQNRKLVQVGIYNGTHVIPNDRKI IWPGET EKPRGYQTGGS

CLAIMS**WHAT IS CLAIMED IS:**

1. A plurality of N-methyl-D-aspartate receptor (NMDAR) antigens coupled to a solid support, wherein the plurality of NMDAR antigens are non-randomly coupled to the solid support.
2. The plurality of NMDAR antigens of claim 1, wherein the solid support comprises a plate, a test tube, a microtiter well, a bead, a slide, a membrane, a microparticle, a nanoparticle, or a chip.
3. The plurality of NMDAR antigens of claim 1 or 2, wherein the solid support comprises plastic, derivatized plastic, polystyrene, polyvinyl chloride, a magnetic metal, a non-magnetic metal, glass, or silicon.
4. The plurality of NMDAR antigens of any one of claims 1 to 3, wherein the plurality of NMDAR antigens comprise the amino acid sequence set forth in any of SEQ ID NOs: 1 to 5.
5. The plurality of NMDAR antigens of any one of claims 1 to 3, wherein the plurality of NMDAR antigens comprise the amino acid sequence set forth in SEQ ID NO: 1.
6. The plurality of NMDAR antigens of any one of claims 1 to 3, wherein the plurality of NMDAR antigens comprise the amino acid sequence set forth in SEQ ID NO: 2.
7. The plurality of NMDAR antigens of any one of claims 1 to 3, wherein the plurality of NMDAR antigens comprise the amino acid sequence set forth in SEQ ID NO: 3.
8. The plurality of NMDAR antigens of any one of claims 1 to 3, wherein the plurality of NMDAR antigens comprise the amino acid sequence set forth in SEQ ID NO: 4.
9. The plurality of NMDAR antigens of any one of claims 1 to 3, wherein the plurality of NMDAR antigens comprise the amino acid sequence set forth in SEQ ID NO: 5.
10. The plurality of NMDAR antigens of any one of claims 1 to 3, wherein the plurality of NMDAR antigens comprise the amino acid sequence set forth in SEQ ID NO: 83.
11. The plurality of NMDAR antigens of any one of claims 1 to 10, wherein the plurality of NMDAR antigens lack an N-terminal signal peptide.
12. The plurality of NMDAR antigens of any one of claims 1 to 11, wherein the plurality of NMDAR antigens do not comprise a GluN2A domain, GluN2B domain, GluN2C domain, GluN2D domain, or combinations thereof of NMDAR.
13. The plurality of NMDAR antigens of any one of claims 1 to 12, wherein the plurality of NMDAR antigens are covalently coupled to the solid support.
14. The plurality of NMDAR antigens of any one of claims 1 to 12, wherein the plurality of NMDAR antigens are noncovalently coupled to the solid support.

15. The plurality of NMDAR antigens of any one of claims 1 to 14, wherein the plurality of NMDAR antigens further comprise an Fc polypeptide.
16. The plurality of NMDAR antigens of claim 15, wherein the Fc polypeptide is attached to the C-terminus of the plurality of NMDAR antigens.
17. The plurality of NMDAR antigens of claim 15, wherein the Fc polypeptide is attached to the N-terminus of the plurality of NMDAR antigens.
18. The plurality of NMDAR antigens of any one of claims 15 to 17, wherein the Fc polypeptide is a murine Fc polypeptide.
19. The plurality of NMDAR antigens of any one of claims 1 to 18, wherein the plurality of antigens comprise an affinity tag.
20. The plurality of NMDAR antigens of claim 19, wherein the affinity tag is coupled to the C-terminus of the plurality of NMDAR antigens.
21. The plurality of NMDAR antigens of claim 19, wherein the affinity tag is coupled to the N-terminus of the plurality of NMDAR antigens.
22. The plurality of NMDAR antigens of any one of claims 19-21, wherein the affinity tag comprises a His tag, a FLAG tag, a c-Myc tag, an HA tag, a V5 tag, a GST tag, a MBP tag, a CBP tag, a CBD tag, an Avi-tag, a biotinylated Avi-tag, or combinations thereof.
23. The plurality of NMDAR antigens of any one of claims 19-21, wherein the affinity tag comprises a biotinylated Avi-tag.
24. The plurality of NMDAR antigens of claim 23, wherein the biotinylated Avi-tag is coupled to a solid support comprising an avidin.
25. The plurality of NMDAR antigens of claim 24, wherein the avidin is deglycosylated avidin (e.g., neutravidin or streptavidin).
26. The plurality of NMDAR antigens of any one of claim 19-21, wherein the affinity tag comprises a His tag.
27. The plurality of NMDAR antigens of either one of claims 22 or 26, wherein the His tag is non-covalently coupled to a solid support comprising nickel.
28. The plurality of NMDAR antigens of claim 27, wherein the solid support comprising nickel is a well of an enzyme-linked immunosorbent assay (ELISA) plate.
29. The plurality of NMDAR antigens of any one of claims 1 to 28, wherein individual NMDAR antigens of the plurality of NMDAR antigens non-randomly coupled to the solid support are separated by an average distance of 15 nm or less.
30. The plurality of NMDAR antigens of any one of claims 1 to 29, wherein the plurality of NMDAR antigens are bound to an anti-NMDAR antibody.

31. The plurality of NMDAR antigens of any one of claims 1 to 29, wherein the plurality of NMDAR antigens are bound to a pathogenic anti-NMDAR antibody.
32. A method of detecting a pathologic anti-NMDAR antibody in a biological sample of an individual, the method comprising contacting the biological sample of the individual to the plurality of NMDAR antigens of any one of claims 1 to 31 and detecting binding of the pathologic anti-NMDAR antibody in the biological sample to the plurality of NMDAR antigens.
33. The method of claim 32, wherein the biological sample comprises blood, plasma, serum, saliva, cell lysate, lymph, amniotic fluid, cerebral-spinal fluid, lachrymal fluid, mucus, urine, sputum, amniotic fluid, or sweat.
34. The method of claim 32, wherein the biological sample comprises blood.
35. The method of claim 32, wherein the biological sample comprises plasma.
36. The method of claim 32, wherein the biological sample comprises serum.
37. The method of claim 32, wherein the biological sample comprises lymph.
38. The method of claim 32, wherein the biological sample comprises cerebral-spinal fluid.
39. The method of claim 32, wherein the biological sample comprises amniotic fluid.
40. The method of any one of claims 32 to 39, wherein the binding of the pathologic anti-NMDAR antibody to the plurality of NMDAR antigens is detected by an enzymatic reaction.
41. The method of any one of claims 32 to 40, wherein the binding of the pathologic anti-NMDAR antibody to the plurality of NMDAR antigens is detected by a fluorescent signal.
42. The method of any one of claims 32 to 41, wherein the binding of the pathologic anti-NMDAR antibody to the plurality of NMDAR antigens is detected by an immunoassay.
43. The method of claim 42, wherein the immunoassay comprises an ELISA.
44. The method of claim 43, wherein the ELISA comprises contacting the biological sample of the individual to the plurality of NMDAR antigens to produce a pathologic anti-NMDAR antibody/NMDAR antigen complex; and contacting the pathologic anti-NMDAR antibody/NMDAR antigen complex to a detection agent that binds to the pathologic anti-NMDAR antibody.
45. The method of claim 44, wherein the detection agent is an anti-isotype antibody.
46. The method of claim 44 or 45, wherein the detection agent is labeled with a fluorescent compound or an enzyme.
47. The method of any one of claims 32 to 41, wherein the binding of the pathologic anti-NMDAR antibody to the plurality of NMDAR antigens is detected by fluorescently activated cell sorting (FACS).

48. The method of any one of claims 32 to 47, wherein the anti-NMDAR antibody present in the biological sample is detected at a concentration of between 0.3 ng/mL - 100 µg/mL.
49. The method of any one of claims 32 to 48, wherein the presence of the pathologic anti-NMDAR antibody indicates a diagnosis of autoimmune encephalitis, dementia, psychosis, schizophrenia, bipolar disorder, seizure, epilepsy, or depression.
50. The method of any one of claims 32 to 48, wherein the presence of the pathologic anti-NMDAR antibody indicates a diagnosis of autoimmune encephalitis.
51. The method of any one of claims 32 to 50, further comprising quantifying a level of the pathologic anti-NMDAR antibody in the biological sample.
52. The method of any one of claims 32 to 51, further comprising generating a report that indicates the presence of or the level of the anti-NMDAR antibody in the biological sample.
53. The method of any one of claims 32 to 52, further comprising administering to the individual a therapeutic anti-NMDAR antibody or an anti-NMDAR binding fragment thereof that prevents binding of the pathologic anti-NMDAR autoantibody to an NMDAR of the individual, based upon detecting the presence of the pathologic anti-NMDAR antibody.
54. The method of claim 53, wherein the therapeutic anti-NMDAR antibody comprises:
a heavy chain variable region (VH) comprising:
a) a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 13;
b) a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 14; and/or
c) a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 15; and
a light chain variable region (VL) comprising:
d) a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 16;
e) a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 17; and/or
f) a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 18.
55. The method of claim 53, wherein the therapeutic anti-NMDAR antibody comprises:
a heavy chain variable region (VH) comprising:
a) a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 23;

- b) a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 24; and/or
 - c) a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 25; and
- a light chain variable region (VL) comprising:
- d) a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 26;
 - e) a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence EDN; and/or
 - f) a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 28.
56. The method of claim 53, wherein the therapeutic anti-NMDAR antibody comprises:
- a heavy chain variable region (VH) comprising:
- a) a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 33;
 - b) a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 34; and/or
 - c) a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 35; and
- a light chain variable region (VL) comprising:
- d) a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 36;
 - e) a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 37; and/or
 - f) a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 38.
57. The method of claim 53, wherein the therapeutic anti-NMDAR antibody comprises:
- a heavy chain variable region (VH) comprising:
- a) a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 43;
 - b) a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 44; and/or
 - c) a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 45; and
- a light chain variable region (VL) comprising:

- d) a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 46;
 - e) a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 47; and/or
 - f) a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 48.
58. The method of claim 53, wherein the therapeutic anti-NMDAR antibody comprises:
a heavy chain variable region (VH) comprising:
- a) a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 53;
 - b) a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 54; and/or
 - c) a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 55; and
- a light chain variable region (VL) comprising:
- d) a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 56;
 - e) a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 57; and/or
 - f) a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 58.
59. The method of claim 53, wherein the therapeutic anti-NMDAR antibody comprises:
a heavy chain variable region (VH) comprising:
- a) a heavy chain complementary determining region 1 (HCDR1) comprising an amino acid sequence of SEQ ID NO: 63;
 - b) a heavy chain complementary determining region 2 (HCDR2) comprising an amino acid sequence of SEQ ID NO: 64; and/or
 - c) a heavy chain complementary determining region 3 (HCDR3) comprising an amino acid sequence of SEQ ID NO: 65; and
- a light chain variable region (VL) comprising:
- d) a light chain complementary determining region 1 (LCDR1) comprising an amino acid sequence of SEQ ID NO: 66;
 - e) a light chain complementary determining region 2 (LCDR2) comprising an amino acid sequence of SEQ ID NO: 67; and/or

- f) a light chain complementary determining region 3 (LCDR3) comprising an amino acid sequence of SEQ ID NO: 68.
60. The method of claim 53, wherein the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region and a light chain immunoglobulin variable region selected from:
- a) SEQ ID NO: 11 and SEQ ID NO: 12,
 - b) SEQ ID NO: 21 and SEQ ID NO: 22,
 - c) SEQ ID NO: 31 and SEQ ID NO: 32,
 - d) SEQ ID NO: 41 and SEQ ID NO: 42,
 - e) SEQ ID NO: 51 and SEQ ID NO: 52, or
 - f) SEQ ID NO: 61 and SEQ ID NO: 62.
61. The method of claim 53, wherein the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 11 and a light chain immunoglobulin variable region comprising an amino acid sequence of SEQ ID NO: 12.
62. The method of claim 53, wherein the therapeutic anti-NMDAR antibody comprises a heavy chain immunoglobulin variable region comprising an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 11 and a light chain immunoglobulin variable region comprising an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO: 12.
63. The method of any one of claims 53 to 62, wherein the therapeutic anti-NMDAR antibody is a one-armed antibody.
64. The method of any one of claims 32 to 63, wherein detecting binding of the pathologic anti-NMDAR antibody in the biological sample comprises detecting binding of an IgG isotype of the pathologic anti-NMDAR antibody.
65. The method of any one of claims 32 to 63, wherein detecting binding of the pathologic anti-NMDAR antibody in the biological sample comprises detecting binding of an IgA isotype of the pathologic anti-NMDAR antibody.
66. The method of any one of claims 32 to 63, wherein detecting binding of the pathologic anti-NMDAR antibody in the biological sample comprises detecting binding of an IgM isotype of the pathologic anti-NMDAR antibody.
67. The method of any one of claims 32 to 63, wherein detecting binding of the pathologic anti-NMDAR antibody in the biological sample irrespective of whether the pathologic anti-NMDAR antibody in the biological sample is IgA, IgM, or IgG.