BIPOLAR DISORDER AND ANTIBODIES AGAINST THE N-METHYL-D-ASPARTATE RECEPTOR: A GATE TO THE INVOLVEMENT OF AUTOIMMUNITY IN THE PATHOPHYSIOLOGY OF BIPOLAR ILLNESS

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ABSTRACT

The high prevalence of comorbidity between bipolar disorder (BD) and other medical conditions, including autoimmune diseases, supports the hypothesis of the nature of BD as a biological illness category. Hence, an immune dysregulation process may play an important role in the development of at least certain subtypes of BD. Increasing evidence also suggests that the N-methyl-D-aspartate receptor (NMDAR) may be relevant in the pathophysiology of BD. A possible key mechanism underlying the physiopathology of

certain autoimmune diseases that may present with affective symptoms might be the production of anti-NMDAR auto-antibodies (auto-Abs). The best characterized autoimmune anti-NMDAR disease is the anti-NMDAR encephalitis. It has been found that 4% of these patients present isolated, mostly affective, psychiatric manifestations during their illness. An interesting suggestion emerged from this overview is that the same mechanisms that trigger affective symptoms in patients with increased anti-NMDAR auto-Abs levels could be involved in the physiopathology of at least a subgroup of BD. Future studies are needed to characterize the relationship between anti-NMDAR auto-Abs and BD.

Keywords: Bipolar disorder, N-Methyl-D-Aspartate Receptor, antibodies, encephalitis, autoimmunity, mania, depression,

Highlights:

- There is a high comorbidity between BD and autoimmune diseases.
- An immune dysregulation may be involved in the development of BD.
- NMDAR dysfunctions may have a relevant role in the pathophysiology of BD.
- Anti-NMDAR auto-Abs may be related with the affective symptoms in autoimmune diseases.
- A subgroup of BD might present increased levels of anti-NMDAR auto-Abs.

1. INTRODUCTION

Bipolar Disorder (BD) is a severe, chronic and recurrent illness, which affects 3% or more of the general population, and characterized by a high morbidity, mortality and significant costs to individuals and society (Catalá-López et al., 2013; Fagiolini et al., 2013; Whiteford et al., 2013)**.** Despite significant advances in our understanding of the underlying neurobiology of BD, effective treatments still represent a demanding clinical challenge (Maletic and Raison, 2014; Vieta et al., 2013). The current clinical management of BD, which is based mainly on a symptom rather than a syndrome approach, has not yet given rise to satisfactory treatments providing a sustained recovery for many patients (Gitlin, 2006; Vieta and Valentí, 2013)**.**

A more complex perspective of the nature of BD as a biological illness category has been recently suggested, based on new evidence derived from genetic, neuroimaging, histological and biochemical studies that bear strong implications in terms of new potential therapeutic targets (Maletic and Raison, 2014). Actually, a high prevalence of comorbidity between BD and other medical conditions, regardless from long-term medication side-effects, has been observed, including metabolic, neurological and autoimmune diseases (Carta et al., 2012; McElroy and Keck, 2014; Rege and Hodgkinson, 2013). Especially, different autoimmune conditions, such as thyroiditis, rheumathoid arthirits and multiple sclerosis are often associated with BD, but the extent to which these comorbidities can underpin a common pathophysiological basis is yet to be ascertained (Benros et al., 2013; Carta et al., 2014; Hamdani et al., 2013). A role for inflammatory mediators and for an immune dysregulation that could be involved in the pathogenesis and progression of the illness has been suggested for several psychiatric disorders (Benros et al., 2014), including BD (Bauer et al., 2014; Berk et al., 2011; Kapczinski et al., 2011).

Recent studies have focused on the role of glutamatergic (GLU) neurotransmission N-methyl-D-aspartate receptors (NMDAR)-mediated (Rosenthal-Simons et al., 2013). Initially, alterations in GLU neurotransmission were found to be associated with schizophrenia and related disorders (Corlett et al., 2011). Afterwards, the interest in NMDAR-mediated GLU transmission has gradually shifted from psychosis to mood disorders (Rosenthal-Simons et al., 2013). Converging evidence derived from genetic, post-mortem, biochemical and imaging studies points towards a major role of GLU and NMDAR dysregulation in the etiopathogenesis of BD (Maletic and Raison, 2014) both during mania and depression (Diazgranados et al., 2010; Zarate et al., 2010). It has been found that BD is characterized by altered levels of GLU, abnormalities in the NMDAR gene expression, concentration and function (Ghasemi et al., 2014). Moreover, it is well known the efficacy of many drugs commonly used in different phases of BD which act as NMDAR modulators, such as lithium, lamotrigine and some atypical antipsychotics (Ramadan et al., 2012; Sourial-Bassillious et al., 2009; Tarazi et al., 2003). Finally, recent evidence has focused on the positive effect of the NMDAR antagonist ketamine for the treatment of resistant bipolar depression (Diazgranados et al., 2010; Zarate et al., 2012).

An autoimmune process involving the NMDAR has been recently outlined as a possible biological correlate of the pathopsysiology of BD in a cohort of 60 manic patients, which presented elevated levels of auto-Abs against the NR2 subunit of the NMDAR (Dickerson et al., 2012). A support for this hypothesis comes from findings on patients suffering from the recent-discovered anti-NMDAR encephalitis. This disease was first described in 2005 (Vitaliani et al., 2005) and is characterized by an encephalitis caused by the presence of auto-Abs against the NR1 subunit of the NMDAR (Dalmau et al., 2008). Usually, most of patients affected by the anti-NMDAR encephalitis have psychiatric manifestations at onset, with predominance of affective symptoms. A study conducted on

a cohort of 571 patients with anti-NMDAR encephalitis revealed that 4% of these patients developed isolated psychiatric episodes, mostly mood disorders (Kayser et al., 2013). The nature and extent of the possible relationship between NMDAR encephalitis, anti-NMDAR auto-Abs and BD is yet to be ascertained.

The aim of this critical overview is to discuss the relevance of NMDAR in the pathophysiology of BD, and the possible evidence of an autoimmune response in some bipolar patients involving the NMDAR. Also, we aim at reviewing the available data regarding the anti-NMDAR encephalitis, given its frequent clinical presentation with mood symptoms. Finally, we discuss the potential clinical and therapeutic implications of our findings.

2. THE ROLE OF NMDA RECEPTORS IN BIPOLAR DISORDER

Increasing evidence suggests that the NMDAR represents a possible target for the neurobiology and treatment of BD (Fountoulakis, 2012; Ghasemi et al., 2014).

The amino acid glutamate is the most abundant excitatory neurotransmitter in the brain and the ionotropic NMDAR is one of the major classes of its receptors. Once activated, NMDAR mediate excitatory neurotransmission through the ion channel, mostly Ca^{++}-mediated (Li and Tsien, 2009; Stephenson et al., 2008). The NMDAR is a heterotetrameric structure which include at least one obligatory subunit, NR1, and different combinations of NR2 (NR2, subtypes A-D) or NR3 (NR3, subtypes A-B) subunits, with multiple binding sites for glutamate, polyamine, Mg^{++} and glycine (Traynelis et al., 2010) (**Fig. 1**). The activation of the NMDAR requires the concomitant depolarization of the membrane with simultaneous binding of the amino acid glycine to NR1 or NR3 subunits and of the glutamate to NR2 subunit, resulting in the opening of the channel, leading to cation (primarly Ca^{++}) influx into the cell (Furukawa et al., 2005). The

activation of the NMDAR starts the signal transduction cascade, which includes the activation of different protein kinases (PK) as PKC, PKA and extracellular signal-regulated protein kinase (ERK) (among other signaling proteins) (Traynelis et al., 2010). The NMDAR activation is involved in the excitatory neurotransmission and it plays a key role in the synaptic plasticity and hippocampal long-term potentiation, which regulates brain processes such as learning and memory (Anwyl, 1999; Li and Tsien, 2009; Stephenson et al., 2008). An excess of glutamate and a subsequent overstimulation of NMDAR is supposed to be one of the most important mediators of excitotoxicity and neuronal death processes through an excessive Ca^{++} influx (Ghasemi et al., 2014; Kalia et al., 2008). In this line, it has been recently hypothesized that chronic stress could induce the NMDAR overstimulation causing an excessive calcium influx and leading to downregulation of the brain-derived neurotrophic factor (BDNF) as a result of the neurotoxic effect of calcium dysregulation (Vásquez et al., 2014).

An association between NMDAR alterations and BD has been reported in early studies which found higher glycine levels in the erythrocytes of BD patients compared to healthy subjects (Rosenblatt et al., 1979)**.** Subsequent research has shown conflicting results, with some studies replicating the increased levels of glycine and glutamate in BD patients (Altamura et al., 1993; Hoekstra et al., 2006), while others reporting decreased levels of glutamate in plasma or cerebrospinal fluid (CSF) of BD subjects (Frye et al., 2007a; Palomino et al., 2007). Further studies using proton magnetic resonance spectroscopy revealed increased levels of glutamate in frontal cortex, basal ganglia, thalamic gray matter and anterior cingulate-medial prefrontal cortex in patients with BD (Castillo et al., 2000; Dager et al., 2004; Frye et al., 2007b). These results have been partially replicated in postmortem studies, with increased levels of glutamate found in the frontal cortex of BD patients (Hashimoto et al., 2007). Neuropathological studies also suggest a reduced

NMDAR-mediated glutamatergic activity in BD patients, specifically slower NMDAR kinetics due to lower contribution of NR2A subunits (Fountoulakis, 2012). Postmortem studies assessing the distribution of NMDAR subunits in BD patients reported conflicting results regarding their expression in different cortical areas and hippocampus (Beneyto et al., 2007; Fountoulakis, 2012; Toro and Deakin, 2005).

Another source of data comes from studies on glutathione. Glutathione is not only an antioxidant but may also act through non-redox mechanisms, either by acting as a reserve pool of glutamate (Koga et al., 2011) or through allosteric control of the NMDAR (Varga et al., 1997). Rosa et al. (2014) recently reported that glutathione levels are lower and more oxidized in bipolar patients as compared to healthy controls.

Finally, some preliminary genetic studies suggested a relationship between genes encoding the NMDAR 1, 2A and 2B subunits and BD, leading to a reduced glutamatergic transmission in these patients (Avramopoulos et al., 2007; Itokawa et al., 2003; Mundo et al., 2003). Nevertheless, such studies are sparse and have not been replicated, highlighting the need for further investigation (Fountoulakis, 2012; Ghasemi et al., 2014).

2.1. NMDA Receptor in Mania

As abovementioned, the activation of the NMDAR starts a signal transduction cascade, which includes the activation of several PK, such as PKC, PKA and ERK among other signaling proteins. Considerable biochemical evidence suggests that the PKC signaling cascade may be a key point for the pathophysiology of manic symptoms (Arnsten and Manji, 2008; Hahn and Friedman, 1999; Turecki et al., 1998; Wang and Friedman, 1996). In preclinical studies, mice treated chronically with a well-known pro-manic drug (amphetamine) presented significantly increased membrane PKC activity in the frontal cortex (Szabo et al., 2009). This finding has been replicated in post-mortem studies in

both brain tissue and peripheral cells of BD patients (Arnsten and Manji, 2008). Similarly, an enhanced PKC-mediated phosphorylation of NMDAR NR1 subunit was found in the prefrontal cortex of sleep-deprived mice -a behavioral model of mania- as well as in those treated with the antidepressant imipramine. These results were in striking contrast to the lithium-treated mice, in which this process was significantly reduced (Szabo et al., 2009). In a manic-like sleep deprivation animal model a decrease of the expression of NR2B subunit of the NMDAR was also found, as well as a reduced activation of ERK (Park et al., 2012).

Further evidence supporting the role of the NMDAR in the etiopathogenesis of mania comes from studies on the effect of "anti-manic" agents extensively used for the treatment of BD. Lithium-mediated inhibition of glutamatergic neurotransmission has been suggested as a possible mechanism of action of this drug (Basselin et al., 2006; Calabrese and Halpain, 2014). Moreover, lithium is able to attenuate the influx of intracellular calcium secondary to NMDAR activation (Sourial-Bassillious et al., 2009). As abovementioned, another supposed mechanism of lithium in modulating the NMDAR is the reduction of PKC activity (Szabo et al., 2009). Despite being structurally different from lithium, valproic acid, another drug commonly used for the treatment of the manic phase of BD, may act by regulating the NMDAR in manic-like animal model (sleep deprivated) by restoring the correct expression of NR2B subunit of NMDAR and the correct activation of ERK, both significantly reduced in sleep deprivate mice (Park et al., 2012).

2.2. NMDA Receptor in Depression

More robust evidence supports the role of NMDAR as a novel target to investigate and treat unipolar and bipolar depression (Vásquez et al., 2014). The strategy of using

NMDAR modulators as antidepressants, specifically the anesthetic ketamine, has taken strength in the past years. Intravenous single ketamine infusion exerts rapid and sustained (1 to 2 weeks) antidepressant effects in both preclinical and clinical studies in patients with treatment-resistant major depressive disorder (MDD) (Aan Het Rot et al., 2012; Berman et al., 2000; Duman et al., 2012; Murrough et al., 2013; Zarate et al., 2006a). Similarly, recent studies have assessed the efficacy of ketamine in resistant bipolar depression with findings similar to those obtained in MDD (Diazgranados et al., 2010; Rybakowski et al., 2013; Zarate et al., 2012). Moreover, ketamine shows a rapid (within 40 min.) antisuicidal effect in bipolar depressed patients, an effect lasting for 3 days after drug infusion (Zarate et al., 2012).

The mechanisms underlying ketamine's antidepressant effect were addressed in preclinical studies. The blocking of NMDAR produced by ketamine would enhance the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPAR) receptor efficiency (Zarate and Manji, 2008). In this sense, ketamine might exert rapid antidepressant effects by enhancing AMPAR relative to NMDAR throughput in critical neuronal circuits (Maeng et al., 2008). Another recent supposed mechanism of ketamine is the inhibition of Ca^{++} influx with a consequent up-regulation and increased synthesis of BDNF (Monteggia et al., 2013; Vásquez et al., 2014).

Other NMDAR channel modulators also showed a rapid onset combined with lasting antidepressant effects. Recently, amidated tetrapeptide (threonine–proline–proline–threonine) GLYX-13, a partial agonist of NMDAR at glycine binding site (Moskal et al., 2005), was found to have similar antidepressant effects as ketamine, without the motor and dissociative side effects (Moskal et al., 2014). Also the AZD6765 (lanicemine), another NMDAR antagonist, was found to act as a rapid antidepressant at a single dose in MDD, also with the absence of dissociative effects (Sanacora et al., 2014;

Zarate et al., 2013). However, this drug's development has been recently discontinued due to negative phase III data. Memantine, a low-affinity, non-competitive, open-channel NMDAR antagonist, has shown conflicting results both in unipolar (Teng and Demetrio, 2006; Zarate et al., 2006b) and bipolar resistant depression (Anand et al., 2012; Koukopoulos et al., 2012, 2010). Finally, it has been found that also the agonism of NMDAR may promote antidepressant effects. Sarcosine, an NMDAR co-agonist at the glycine binding site (Zhang et al., 2009), showed an antidepressant effect in both rats and patients with depression (Huang et al., 2013). Among mood stabilizers with antidepressants properties, lamotrigine has been found to inhibit NMDAR-mediated signalling involving the arachidonic acid cascade, generally up-regulated in the post-mortem BD brain (Ramadan et al., 2012).

Globally, the available evidence supports the hyphothesis that NMDAR may play an important role in the pathophysiology of BD. However, available studies present important limitations and many questions remain still unaddressed. Future research is necessary to elucidate the mechanisms underlying BD and its possible relation to NMDAR dysfunction, and to explore possible NMDAR-targeted novel therapeutic agents.

3. AUTOIMMUNITY, BIPOLAR DISORDER AND NMDA RECEPTOR

Increasing evidence suggests that an immune dysregulation may play some role in the development and neuroprogression of BD (Rege and Hodgkinson, 2013).

In particular, available data support a relationship between autoimmunity and BD. Sidhom et al. (2012) have found that BD patients have significantly more auto-Ab compared to other psychiatric patients and to healthy controls. A large cohort study reported that non-specific autoimmune processes could precede the onset of BD (Eaton et

al., 2010). Furthermore, it is quite known that certain autoimmune diseases, such as the neuropsychiatric systemic lupus erythematosus (NPSLE), Hashimoto's Thyroiditis and Multiple Sclerosis (MS) are often associated with symptoms of mania and depression (Carta et al., 2014; Rege and Hodgkinson, 2013). For example, among neuropsychiatric symptoms of NPSLE, mood disturbances are highly prevalent (69-74%) (Popescu and Kao, 2011). Similarly, several reports indicate that Hashimoto's autoimmune thyroiditis may presents with affective symptoms and cognitive dysfunctions (Bocchetta et al., 2007; Canelo-Aybar et al., 2010; Liu et al., 2011; Müssig et al., 2005).

Regarding the pathophysiology of some of these disorders, growing evidence suggests an involvement of the glutamate pathway (Rege and Hodgkinson, 2013). It has been hypothesized that a key mechanism underlying the physiopathology of NPSLE and contributing to the presence of cognitive dysfunctions and affective symptoms might be the production of anti-dsDNA Ab that cross-react with the NMDAR NR2 subunit (DeGiorgio et al., 2001; Mak et al., 2009). In the same line, antibodies against the NMDAR NR2B subunit have found to be present in psychiatric patients with antithyroid antibodies increased levels (Chiba et al., 2013).

Another recently discovered, NMDAR-mediated autoimmune disease, which is almost always associated with psychiatric symptoms and which could be related to BD is the anti-NMDAR encephalitis.

4. THE ANTI-NMDA RECEPTOR ENCEPHALITIS

Anti-NMDAR encephalitis is an autoimmune disease in which IgG auto-Abs are produced against the NR1 subunit of the NMDAR. The disorder was originally discovered in 2005 (Vitaliani et al., 2005), and it may be associated with an underlying

tumor, usually a teratoma, whose frequency depends from several factors, including age, sex, and gender (Florance et al., 2009; Titulaer et al., 2013a).

Anti-NMDAR encephalitis predominates in young adults and children (Dalmau et al., 2008; Irani et al., 2010; Titulaer et al., 2013a; Viaccoz et al., 2014). In young adults, females are more frequently affected than males (4:1 ratio). Although the incidence of anti-NMDAR encephalitis is still unknown, epidemiological studies suggest that this syndrome is the most common cause of autoimmune encephalitis after acute demyelinating encephalomyelitis (ADEM) (Gable et al., 2012; Granerod et al., 2010).

As the onset of anti-NMDAR encephalitis commonly occurs with psychiatric symptoms, the scientific interest of psychiatry for this disease has grown during the last years (Chapman and Vause, 2011; Kayser et al., 2010).

4.1. The role of Autoantibodies in the Anti-NMDA Receptors Encephalitis

The pathogenesis underlying anti-NMDAR encephalitis is quite well studied. In vitro studies with cultures of dissociated rat hippocampal neurons show that patients' auto-abs bind to the receptors and produce a highly selective decrease of the density of receptors at synaptic and extrasynaptic sites accompanied by a decrease of NMDAR-mediated synaptic currents. These effects result from Ab-mediated cross-linking of the receptors and subsequent internalization. The effects are reversible upon removing the Abs from the media (Hughes et al., 2010; Mikasova et al., 2012). A similar decrease of the density of NMDAR has been demonstrated in the brain of autopsied patients (Hughes et al., 2010). Similar Ab-mediated effects have been demonstrated in an animal model in which the cerebroventricular infusion of patients' Abs to mice resulted in a dramatic decrease NMDAR levels accompanied by memory loss and anhedonic and depressive behaviours. In this model, the behavioral effects progressively reversed after stopping the infusion of

patients' Abs and this clinical improvement was accompanied by restoration of the levels of NMDAR (Planagumà et al., 2014). In vitro studies showed that, in order to compensate the effects of patients' antibodies, neurons engage homeostatic synaptic plasticity mechanisms consisting in a decrease of inhibitory synaptic transmission into excitatory hippocampal neurons (Moscato et al., 2014).

The mechanism that triggers the auto-Ab production is not completely understood. Teratoma tissues removed from patients affected by anti-NMDAR encephalitis show atypical nervous tissue with the presence of ectopic NMDAR, which could trigger an autoimmune reaction. However, many patients do not have an underlying teratoma (Titulaer et al., 2013a). An alternative hypothesis is the induction of an autoimmune process triggered by a previous infection, such as a viral exposure. Recently, several studies have suggested a link between herpes simplex virus and anti-NMDAR encephalitis (Armangue et al., 2014; Titulaer et al., 2014).

4.2. Clinical Presentation

The progression of the disease is highly predictable (Titulaer et al., 2013a). Patients often have a prodromal syndrome resembling a viral process, followed a few days later by prominent psychiatric symptoms, characterized by emotional changes, behavioural disturbances, fear, cognitive impairment, attention and memory problems, mood disturbances (both depression and mania) and psychosis with delusional thoughts and hallucinations. These symptoms are usually followed by abnormal movements (orofacial dyskinesias, limb and trunk dyskinesias, choreoathetosis, balismus, dystonic postures, rigidity, or opisthotonos), decreased level of consciousness, variable levels of autonomic instability (hyperthermia, fluctuations of the blood pressure, tachycardia, bradycardia, sialorrhea), and sometimes central hypoventilation. Insomnia is very frequent at early

stages of the disease. Seizures may occur at any time during the development of the syndrome. In children, the initial symptom presentation is often characterized by seizures or abnormal movements, which are usually followed by a similar constellation of symptoms as in the adults.

4.3. Diagnosis

An early clinical diagnosis of anti-NMDAR encephalitis can be challenging since at this stage symptoms are non-specific. As mentioned previously, psychiatric symptoms may constitute the initial presentation of the disease, thus leading to a misdiagnosis of having a primary psychiatric disorder.

Magnetic resonance is unremarkable in 60% of patients, while the remainder shows T2 or FLAIR hyperintensity in non-specific regions (Titulaer et al., 2013a). The EEG is usually abnormal, exhibiting non-specific slow disorganized activity, sometimes interspersed with seizure patterns (Dalmau et al., 2008). In 30% of the patients the EEG shows a highly characteristic pattern named "extreme delta brush" (Schmitt et al., 2012).

For these reasons, the diagnosis depends on the clinical recognition of the syndrome with subsequent confirmation of the presence of antibodies to the NR1 subunit of the NMDAR in patient's CSF (serum can give false positive or negative results in ~15% of the cases).

4.4. Treatment and Outcome

Once the diagnosis of anti-NMDAR encephalitis is strongly suspected, the search of an underlying tumor should be initiated. The extent of this search varies according patients' age. While approximately 50% of young females have an underlying ovarian teratoma, the presence of a tumor is rare in young children and young males. In patients older than 45 years, the frequency of a tumor (rarely teratoma) is 23% (Titulaer et al., 2013a,

2013b). In addition patients should start immunosuppressive treatment which usually includes first-line therapies such as steroids, intravenous immunoglobulins, or plasma exchange. If patients do not respond to these treatments, second line therapies include rituximab and cyclophosphamide (Titulaer et al., 2013a). Generally, it has been found that Abs levels tend to be higher in patients with poor outcome compared to those with good outcome (Gresa-Arribas et al., 2014).

Usually, patients affected by anti-NMDAR encephalitis respond well to immunotherapy, especially if it is started promptly. Overall, about 80% of the patients substantially improve or recover (Dalmau et al., 2011, 2008; Titulaer et al., 2013a). Recovery is often accompanied by a decrease in serum and CSF Abs (Gresa-Arribas et al., 2014).

5. THE ROLE OF ANTIBODIES AGAINST NMDA RECEPTOR IN PSYCHIATRY

As previously mentioned, the vast majority of patients affected by Anti-NMDAR encephalitis starts with psychiatric symptoms, so much that such subjects might be initially misdiagnosed as primarily psychiatric patients.

On this basis, over the last years it has been hypothesized that 1) a subset of primarily psychiatric patients, not affected by anti-NMDAR encephalitis, might have Ab against the NMDAR, and possibly they might respond to immunotherapy, or that 2) there is a subset of patients affected by anti-NMDAR encephalitis which presents, during certain periods of their illness, pure psychiatric symptoms, with no neurological symptoms (Dickerson et al., 2012; Hammer et al., 2014; Haussleiter et al., 2012; Kayser et al., 2013; Masdeu et al., 2012; Pearlman and Najjar, 2014; Pollak et al., 2014; Rhoads et al., 2011; Steiner et al., 2013; Zandi et al., 2011).

In order to address the latter point, Kayser et al. (2013) have conducted a study in a cohort of 571 patients with anti-NMDAR encephalitis, with the aim of determining the frequency and type of isolated psychiatric symptoms at illness onset or during relapses. It was found that 4% of patients (N=23) had periods of illness with only psychiatric episodes, occurring in association with the presence of anti-NMDAR auto-Abs in CSF (and sometimes serum) without neurological involvement. In 5 of them, isolated psychiatric symptoms represented the onset of the disease, leading to a treatment delay that could reach 60 weeks. The remaining 18 patients experienced isolated psychiatric episodes during relapses. In patients with isolated psychiatric episodes, the clinical picture was typically dominated by psychotic symptoms with a mood component.

Regarding the first point, there is growing interest in investigating the role of serum anti-NMDAR auto-Abs in psychiatric disorders with possible pathophysiological and clinical implications of this association.

To date, few studies assessing this topic have been conducted in schizophrenia and other psychotic disorders with not remarkable results (Hammer et al., 2014; Haussleiter et al., 2012; Masdeu et al., 2012; Pollak et al., 2014; Rhoads et al., 2011; Steiner et al., 2013; Zandi et al., 2011), while little but potentially attractive evidence on the specific role of anti-NMDAR auto-Abs in BD has been recently reported (Dickerson et al., 2012).

Pollak et al. (2014) have recently published a systematic review and meta-analysis of a total of 7 studies (N=1441) aiming at investigate the prevalence of auto-Abs against the NMDAR (NR1 subunit or the heterodimer NR1/NR2) in psychotic patients (schizophrenia and related psychoses). The authors found no significant differences between cases and controls regarding the overall prevalence of any type of anti-NMDAR auto-Abs; when only IgG Ab were considered, the prevalence was significantly higher in psychotic patients compared to controls. Another recent meta-analysis on the association

between anti-NMDAR auto-Abs and different psychiatric disorders (schizophrenia, schizoaffective disorder, BD and MDD) which included a total of 9 studies (Pearlman and Najjar, 2014), found that psychiatric patients had globally a three times greater likelihood to have increased anti-NMDAR auto-Abs serum levels (IgG, IgM and IgA Ab classes, against NR1, NR1/NR2B and NR2A/NR2B subunits) compared with healthy controls, but rarely against NR1 subunit alone.

To date, despite affective symptoms are frequently reported in patients with anti-NMDAR encephalitis, there is only one relevant study on the possible role of anti-NMDAR auto-Abs in BD (Dickerson et al., 2012), in which serum levels of auto-Abs against the NR2 NMDAR subunit were measured in 60 bipolar and schizoaffective patients during a manic episode compared to 295 psychiatric controls (first psychotic episode, schizophrenic, non-manic bipolar patients) and 170 healthy controls. Measures were performed at three time points in the manic sample (at baseline, at 2-6 days from baseline, and at six months follow-up) and only at baseline in the other groups. Manic patients had significantly increased levels of auto-Abs anti NR2 subunit compared to controls at baseline and at 2-6 days from baseline, while no significant differences were found at 6-months follow-up amongst the two groups. Interestingly, within the manic sample, there was a significant decrease in Abs serum levels across the three study points.

6. DISCUSSION

The current research on the pathogenesis of BD seems to be increasingly more directed towards a relevant biological basis of the illness.

The available evidence suggests that inflammation and an immune dysregulation may be involved in the etiology and neuroprogression of BD (Hamdani et al., 2013; Rege and

Hodgkinson, 2013). In particular, a link between immune dysregulation, autoimmunity and BD has been strongly hypothesized, even if more robust data are needed to confirm these findings. As abovementioned, a comorbidity between BD and different autoimmune diseases has been found in several studies (Carta et al., 2014; Rege and Hodgkinson, 2013). These findings could support the hypothesis that BD and such diseases may share common pathophysiological pathways such as an immune-inflammatory imbalance. Actually, several studies have found increased levels of auto-Abs in BD patients compared to healthy controls (Eaton et al., 2010; Sidhom et al., 2012).

On the other hand, the available data have shown that NMDAR dysfunctions may have a relevant role in the pathophysiology of both depression and mania, thus constituting a possible new target in the treatment of BD. In this line, an interesting suggestion emerged from this overview is that an autoimmune process associated to the presence of auto-Abs against different subunits of the NMDAR could be involved somewhat in the pathogenesis of BD. While it is obvious that NMDAR encephalitis is a rare disease that starts with psychiatric symptoms but always ends up with severe neurological manifestations, and therefore its connection to BD can be labelled at most as "indirect", it is also true that the prominence of mood symptoms, the increased incidence of other autoimmune diseases, and the role of glutamate and its receptors in treatment response in affective disorders indicate that NMDAR are involved in the pathophysiology of BD. The precise mechanisms behind that association are yet to be elucidated.

To date, several studies have been published in order to evaluate the hypothesis that patients affected by primary psychoses (schizophrenia and related psychosis) may harbour anti-NMDAR auto-Abs, with no remarkable results (Hammer et al., 2014; Haussleiter et al., 2012; Masdeu et al., 2012; Pollak et al., 2014; Rhoads et al., 2011;

Steiner et al., 2013; Zandi et al., 2011). To our knowledge, there is only one relevant study which found increased levels of auto-Abs against the NR2 NMDAR subunit in bipolar and schizoaffective patients during a manic episode compared to other psychiatric patients and healthy controls (Dickerson et al., 2012). Interestingly, in this study the levels of auto-Abs decreased across the manic episode, suggesting a possible role of anti-NMDAR auto-Abs as a state marker of acute episode, similarly to that found for BDNF (Cunha et al., 2006; Grande et al., 2014).

Actually, the interpretation of the results and the real pathogenic effect of the presence of anti-NMDAR auto-Abs in psychiatry is difficult to determine due to several limitations of the available studies, such as the lack of examination according to the immmunoglobuline subtype (IgG, IgA, IgM), the type of target antigen (NR1 or NR2) and the type of technique used to determine the antibodies (Kayser and Dalmau, 2014; Leypoldt et al., 2014). Regardless of the technique used, if the antibodies are not visible with immunocytochemistry with live neurons, the significance may range from a non-pathogenic epiphenomenon to the possibility that the primary target is not the NMDAR but a protein sharing a limited epitope sequence with the NMDAR. To date, the only NMDAR Auto-Abs that fulfils criteria of pathogenicity are those associated to anti-NMDAR encephalitis (Hughes et al., 2010; Planagumà et al., 2014)

It has been reported that the presence of anti-NMDAR auto-Abs could be related with the affective symptomatology that often accompanies different autoimmune diseases, such as NPSLE and autoimmune thyroiditis (Chiba et al., 2013; DeGiorgio et al., 2001; Mak et al., 2009). Specifically, the anti-NMDAR encephalitis may represent the paradigm of this association. It has been found that 4% of patients suffering from this disease present isolated psychiatric manifestations during their illness, with a predominance of mood symptoms (mania, depression, lability and impulsivity). Remarkably, 83% of these

patients had a full or substantial recovery from psychiatric symptoms after treatment with immunotherapy (Kayser et al., 2013).

On the basis of the above, it could be assumed that at least one subgroup of bipolar patients might reveal a primary autoimmune process as a potentially underlying pathogenetic mechanism of the illness and present increased levels of anti-NMDAR auto-Abs. An overall proposed model which illustrates the possible physiological consequences on mood of auto-Abs binding and some drugs to the receptor is shown in **Fig. 2**.

Future longitudinal studies are needed to further characterize the relationship between anti-NMDAR auto-Abs and BD in the absence of other autoimmune diseases and the potential pathophysiological, clinical and therapeutic implications of this association.

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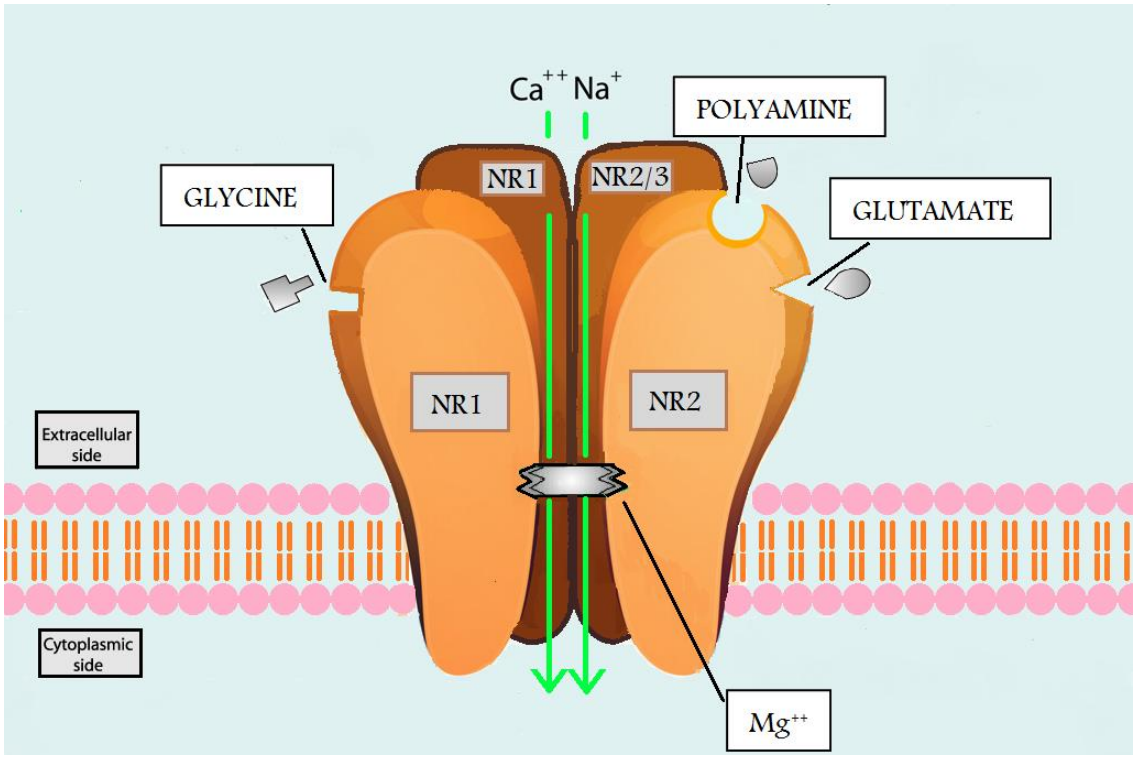
Figure caption

Figure 1. NMDA receptor complex and its binding sites.

Figure 2. An autoimmune process NMDAR-mediated has as a possible biological correlate of the pathophysiology of mood symptoms in BD and the role of pharmacotherapy

A) The presence of Anti-NMDAR auto-Abs may cause a dysfunction of NMDAR (1), leading to an increased Ca^{++} influx (2) and consequent alterations of the signal transduction cascade with increased PKC (3) and other signal proteins activities (4,5). This mechanism could be responsible of the development of mood symptoms in BD (6).
B) The rapid antidepressant effect of ketamine is apparently linked to the blockade of NMDAR (1) and to the enhancement of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) efficiency (2), leading to a regulation of Ca++ influx with a consequent up-regulation and increased synthesis of the Brain-Derived Neurotrophic Factor (BDNF) (3). Several "pro-manic" drugs, such as amphetamine, may act by producing an increased PKC activity (4). Lithium and valproate could act by reducing Ca++ influx secondary to NMDAR activation auto-Abs-mediated (5), and through the stabilization of PKC (lithium) and ERK (valproate) activity (6).



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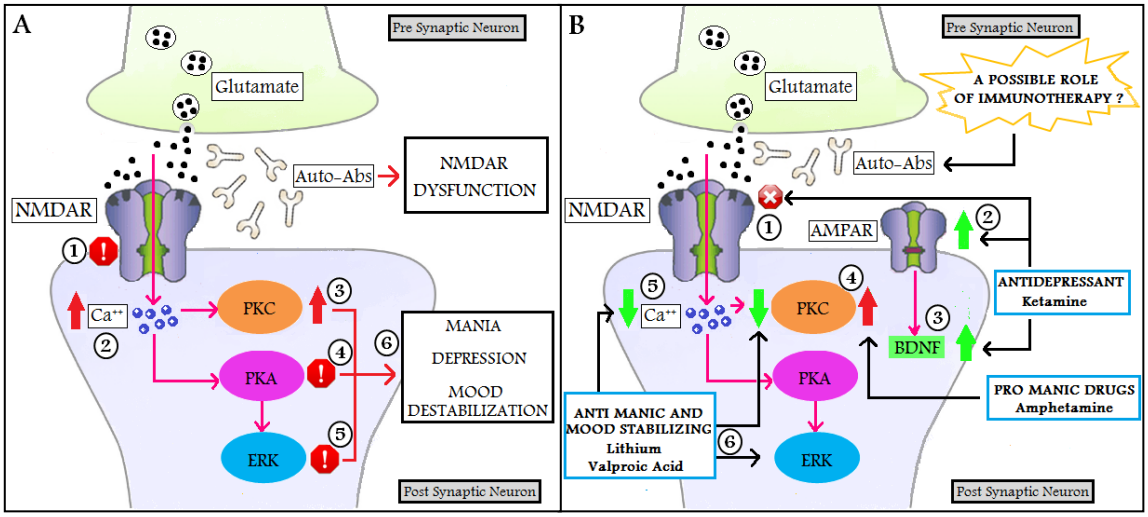

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