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# Catatonia as a Syndrome Characterized by GABAergic Interneuronal Dysfunction Mediated by NMDA Receptors

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Authors RGB and LG wrote the part of manuscript, reviewed and edited the study. Author AM designed the study, wrote the first draft and managed the literature searches. All authors read and approved the final manuscript.*

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## ABSTRACT

Efforts to elucidate the pathophysiology of catatonia have hitherto been unsuccessful largely due to its variegated clinical presentation and seemingly disparate treatment modalities. Catatonia manifests with marked behavioral and cognitive changes, often producing a significant decrease in speech and motor output. Generally, catatonia can be treated with GABA-agonists with impressive symptomatic relief. ECT is also used as a second-line therapeutic intervention if GABA-agonists fail to produce significant symptomatic relief. However, there is uncertainty regarding additional treatment if the aforementioned therapeutic interventions fail to provide symptomatic relief. In the present paper, suggest utilizing pharmacotherapy that modulates NMDAR activity on the basis that

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catatonia can be fundamentally a syndrome characterized by excessive glutamatergic stimulation of NDMAR on cortical GABAergic interneurons leading to a dysregulation of horizontal and vertical processing.

*Keywords: Catatonia; NMDAR; GABA; glutamatergic.*

## 1. INTRODUCTION

Catatonia is generally regarded as a behavioral syndrome characterized by a marked inability to speak or move which is different from the individual's baseline [1]. Within psychiatric nosology, catatonia is not treated as an independent disorder, rather it is considered a condition secondary to some underlying psychiatric or medical condition. [1] However, controversy exists as to whether or not catatonia ought to be considered a diagnosis in and of itself due to the likelihood that catatonia has a distinct neurobiological foundation from the disorder for which it is associated [2]. For instance, irrespective of its etiology, the main features of catatonia are largely equivocal, viz. the patient typically presents with at least three of the following symptoms: stupor, cataplexy, waxy flexibility, negativism, mutism, posturing, mannerism, stereotypy, agitation, grimacing, echolalia and echopraxia [2,3].

Differential diagnosis of patients presenting with symptoms associated with catatonia includes pathologies with overlapping symptomatology, e.g. acute delirium, Parkinson disease, drug toxicity, conversion disorder, etc. As such, it is imperative that the patient is evaluated by neurology, medicine and psychiatry before ultimately concluding that catatonia is the diagnosis. In fact, psychiatric conditions are associated with only a fraction of reported catatonia cases so a thorough medical workup is warranted [4].

Given the spectrum of disorders associated with catatonia, it should be unsurprising that there exist several hypotheses regarding the neurobiological foundation of catatonia. We will present two probable hypotheses regarding the mechanism of catatonia and then present a more nuanced hypothesis regarding its neurobiologic pathophysiology. Finally, we will conclude with some final remarks regarding possible treatment and further research.

[1] *Notably the DSM 5 recognizes a "catatonia not otherwise specified" which allows for the rapid diagnosis and specific treatment of catatonia in severely ill patients for whom the underlying diagnosis is not immediately available.*

The first hypothesis we will consider holds that catatonia involves a "top-down modulation" dysfunction wherein either cortical neurons fail to properly feedback on basal ganglia neurons or basal ganglia neurons fail to feedforward to cortical neurons [3]. We will refer to this thesis as the top-down conjecture. The said conjecture has been associated with a poverty of GABAergic stimulation which serves as the principle modulatory neurotransmitter. Hence, a brain bereft of sufficient GABAergic stimulation is a brain bereft of sufficient top-down modulation. At least superficial evidence for the top-down conjecture is that GABA agonists provide significant, if not complete, symptom improvement [5,6,7].

The second hypothesis we will consider is that in addition to hypoactive dopaminergic and GABAergic activity, cholinergic and serotonergic rebound causes catatonia [8]. Observation that catatonia can be caused by clozapine withdrawal helped to form the rebound conjecture. The fact that catatonia can be treated with atypical antipsychotics, including clozapine, olanzapine, and risperidone, suggests a possible role of 5-HT2 antagonism in the treatment of catatonia as these drugs antagonize both serotonin and dopamine [9,10,11]. Dopamine's role in catatonia has long been established with wide evidence showing that first generation antipsychotics can either cause catatonia or worsen catatonia symptoms. Furthermore, it has been shown that dopaminergic agonists, such as those found in the stimulant class of medications, can treat catatonia symptoms in bipolar and/or depressed patients [12,13,14,15].

The hypothesis that we posit is a modification of the top-down conjecture, viz. the mechanism of catatonia seems to be in a failure of top-down modulation, and the neurobiological bases of this is an excessive simulation of NMDARs found on GABAergic cortical interneurons and pyramidal glutaminergic neurons.

## 2. MATERIALS AND METHODS

A comprehensive systematic review of the literature regarding the treatment of catatonia

was used to inform our hypothesis. Our search strategy served to identify all published randomized trials and all ongoing research into the mechanism of catatonia. For the literature review, we used standard search strategies involving the querying of two online databases (Medline and Cochrane) using key words (catatonia and NMDA, catatonia and GABA, catatonia and mechanisms), followed by evaluation of the bibliographies of relevant articles.

## 3. DISCUSSION

NDMAR Antagonists as a Treatment for Catatonia.

Recent evidence suggests that cortical GABAergic interneurons play an intermediary role between deeper cerebral structures such as the basal ganglia and higher cortical neurons found in the cortex [16,17]. These crucial GABAergic neurons express N-Methyl-D-Aspartic receptors (henceforth NDMAR) and release GABA following glutaminergicstimulation. The NMDAR is an ionotropic glutamate receptor that consists of a heterotetramer of two NR1 and two NR2 subunits, and mediates excitatory post-synaptic potentials [18]. [2] NMDARs require occupation by two types of agonists for their activation, viz.a glutamate site agonist at NR2 subunits and a glycine site agonist at NR1 subunits. NMDARs are distributed widely throughout the nervous system and seem to function in both horizontal and vertical processing [19,20].

A particularly unusual property of NMDAR channels is their high Ca2+ permeability, which endows NMDARs with profound physiological and pathological significance [21]. Simultaneous pre- and post-synaptic activity stimulates Ca2+ influx through NMDARs, activating a variety of intracellular signaling pathways with diverse physiologic consequences. For instance, NMDAR activation on postsynaptic pyramidal neurons in the cerebral cortex leads to the release of glutamate and subsequent downstream neuronal activation. NMDAR activation on GABAergic interneurons, however, results in a release of GABA with subsequent downstream inhibitory effects. Therefore, activation of NMDARs on pyramidal neurons leads to further release of glutamate, thereby providing excitatory stimulation; whereas activation of NMDARs on interneurons leads to GABA release with subsequent inhibitory stimulation [22,23]. GABAergic and glutamanergic stimulation must therefore be in sufficient balance in order for the brain to properly filter and sort input. The sorting of input through GABAergic interneurons and cortical pyramidal neurons seems to play a foundational role in horizontal and vertical processing. Thus, we believe, a dysfunction in the proper interplay between cortical pyramidal neurons and GABAergic interneurons will lead to a failure of said processing and therefore a resultant catatonic state. We further suggest that improper NMDAR activation can lead to catatonia by causing diffuse activation of the GABAergic and glutamatergic systems.

Given the presence of NMDARs on both of the key groups of neurons associated with horizontal and vertical processing, it makes logical sense to investigate their role in the pathophysiology of catatonia. It is widely known that NMDARs can have vastly deleterious effects on neurons if they are excessively activated by glutaminergic signaling [22,23]. Initially, excessive glutaminergic signaling may cause `noise' which disrupts the neural modulation of horizontal and vertical processing. If the excessive stimulation of NMDARs continues, a resultant excitotoxic effect will occur in the neuron, and the neuron will subsequently die.

Interestingly, excessive glutaminergic stimulation of NMDARs is particularly problematic for GABAergic neurons. GABAergic neurons have far more NMDARs than do other populations of neurons leaving them particular vulnerable to excitotoxic damage. As such, excessive NMDAR activation will first lead to dysfunction of these GABAergic neurons, which may present as catatonia. If the excessive glutaminergic stimulation is not resolved, excitotoxic damage will occur and a resultant treatment resistant catatonia will develop. It is, therefore, imperative that catatonia be diagnosed early and treated quickly before such a state arises [24,25,26,27,23].

NMDAR antagonists should therefore be considered as a therapeutic intervention for catatonia when standard GABAergic therapy does not provide clinically appreciable symptom relief. Antagonism of the NMDAR should therefore attenuate the excessive glutamatergic

[2] *Note the literature suggest that there are three families of NMDAR subunits NR1, NR2 and NR3. However, NR3 subunits are not obligatory and modulate NMDAR properties.*

stimulation of the GABAergic neurons which we postulate are primarily involved in the pathophysiology of catatonia. Prospective open-label studies as well as case series suggest that initial treatment with benzodiazepines (BZD) ought to be administered for patients with nonmalignant catatonia, whether the behavioral phenotype be retarded or excited [25,26,27]. We believe that the reason why BZD therapy is successful in resolving catatonia lies in their positive allosteric modulation of the GABA-A receptor.

The GABA-A receptor is a ligand-gated chloride-selective ion channel. BZDs bind to the pocket created by the α and γ subunits and induce a conformational change in the GABA-A receptor, allowing GABA to bind. This modulation of the GABA-A receptor causes what little GABA is evaluable in the synaptic cleft to cause hyperpolarization. We hypothesize that the initial diffuse NMDAR activation on GABAergic interneurons vastly reduces the amount of GABA available in the synaptic cleft. BZDs therefore potentiate GABAergic hyperpolarization through positive allosteric modulation of the postsynaptic GABA-A receptor [28].

An obvious question should therefore be addressed utilizing our model of catatonia, namely why is it the case that GABA-agonists are so strikingly successful in treating some cases of catatonia while useless in the others [29,30,31]? The answer to the said query seems to lie in the duration for which NMDARs are pathologically activated. In cases of initial NMDAR dysfunction without significant excitotoxic damage, restoring basal level of GABA in the brain with GABA agonists will resolve the modulatory failure [32,33,34]. We hypothesize that the temporary restoration of the GABAergic modulation system may allow the neural circuits to accommodate to the pathologic glutaminergic signaling through neuroplastic mechanisms.

Cases in which GABA-agonist seems to fail are cases in which the patient has had catatonia for a greater period of time [24]. In such cases, GABA agonists perhaps would not work because the excessive glutaminergic signaling resulted in irreversible excitotoxic damage to the GABAergic interneuronal modulatory system. In cases of significant neural necrosis, very few drugs would provide much relief. NMDAR antagonists, however, have been shown to resolve some symptoms of catatonia when GABA agonists fail to provide therapeutic relief. However, even NMDAR antagonists must be used antecedent to severe excitotoxic damage. We suggest that these NMDAR antagonists are (i) reducing the noise from excessive glutaminergic signaling and (ii) allowing neuroplastic changes to accommodate for the pathologic glutaminergic stimulation.

## 4. CONCLUSION

We suggest that the mechanism of catatonia therefore lies manifest in the proper activation of NMDARs. Excessive NMDAR activation, a problem for which GABAergic interneurons are far more sensitive given the preponderance of their NMDARs, leads to a 'glutaminergic noise' that prevents sufficient modulation of horizontal and vertical processing leading to catatonia symptoms. Through sufficient modulation of NMDARs, catatonia can be resolved and patients can expect significant, if not complete, symptomatic relief.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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