

Catatonia and the immune system: a review

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Summary

Catatonia is a psychomotor disorder featuring stupor, posturing, and echophenomena. This review examines the evidence for immune dysregulation in catatonia. Activation of the innate immune system is associated with mutism, withdrawal and psychomotor retardation, which constitute the neurovegetative features of catatonia. There is some sparse and conflicting evidence for acute phase activation in catatonia, but it is unclear whether this is secondary to immobility. Various viral, bacterial and parasitic infections have been associated with catatonia, but it is preferentially CNS infections that cause it. The most common cause of autoimmune catatonia is *N*-methyl-*D*-aspartate receptor (NMDAR) encephalitis, which can account for the full spectrum of catatonic features. Autoimmunity appears to cause catatonia less by systemic inflammation but rather by the downstream effects of specific actions on extracellular antigens. The specific relationship to NMDAR encephalitis supports a hypothesis of glutamatergic hypofunction in catatonia.

1. Introduction

Catatonia is a psychomotor disorder characterised by diverse clinical signs, including mutism, negativism, ambitendency, stereotypy, posturing, waxy flexibility, and echophenomena.¹ It is reviewed elsewhere in this issue by Walther and colleagues. Understanding the pathophysiology of this severe disorder is critical given its high rates of medical complications, including pressure ulcers, infections and venous thromboembolism.² Moreover, such understanding may shed light on other neuropsychiatric disorders.

Although catatonia has numerous possible symptom combinations,^{3,4} there are compelling reasons to study it as a single entity. Clinical and demographic factors can distinguish catatonia from other psychotic and affective disorders.⁵ Different forms of catatonia (Kahlbaum's classical retarded catatonia, malignant catatonia and neuroleptic malignant syndrome) are highly comorbid.¹ In terms of treatment, response rates to benzodiazepines and electroconvulsive therapy (ECT) are high, regardless of the aetiology of the catatonia.^{6,7} Moreover, catatonia is not a common disorder, so pragmatically to study it in depth it is helpful to consider it as a whole.

Immune dysregulation is gaining interest as a pathophysiological mechanism underlying neuropsychiatric disorders as diverse as narcolepsy, some dementias, depression, and psychosis, with converging evidence from biochemical, neuroimaging, genetic, and post-mortem studies.^{8,9}

Roles for both the innate immune system, which concerns the rapid, undirected response to pathogen- or injury-associated signals, and the adaptive immune system, which functions over a longer timescale and involves the selection and maturation of antigen-specific T-cell and B-cell mediated responses, have been identified.

In this review, we discuss the evidence for the involvement of the immune system in catatonia. This appears to be a valuable line of enquiry, given the wide range of infective and inflammatory conditions that can cause catatonia (Tables 1 and 4). The approach has some historical precedent, as fever therapy was used to treat psychiatric complications of neurosyphilis in the early 20th Century and, although there are no reported cases of it being used purposefully to treat catatonia, there are examples of patients with catatonia recovering following an intercurrent febrile illness.¹ Subsequently, there were reports of anti-brain antibodies inducing catatonic behaviour in Rhesus monkeys,¹⁰ although these findings were never convincingly replicated.¹¹ Encephalitis lethargica, a sleep and movement disorder with marked similarities to catatonia, has been considered by some to be related to an influenza pandemic.¹² Periodic catatonia, a recurrent form of the illness first described in 1932³⁶¹, has recently been found to have a genetic basis with linkage to the 15q15 locus, an area with an important immunoregulatory role.^{363,364}

This review addresses whether the immune system plays a role in catatonia, using some direct and some more circumstantial evidence and endeavours to establish specific models for this. We consider immunity in terms of innate and adaptive systems for the purposes of clarity, whilst acknowledging that strictly demarcating the two is not always possible.

2. Innate Immune System

2.1 Catatonia due to infection

Table 1: Systematic review of infective causes of catatonia (see box 1 for search criteria)

Infective cause	n	Suspected organisms	n with laboratory evidence of specific organism
Bacterial meningitis / encephalitis	5	<i>Borrelia burgdorferi</i> (4) ¹³⁻¹⁶ , unspecified (1) ¹⁷	4

Viral meningitis / encephalitis	26	<i>Adenovirus</i> (1) ¹⁸ , <i>Cytomegalovirus</i> (1) ¹⁹ , <i>Coronavirus</i> (1) ²⁰ , <i>Epstein Barr virus</i> (1) ²¹ , <i>HHV6</i> (1) ²² , <i>Herpes simplex virus</i> (8) ²³⁻³⁰ , <i>Japanese encephalitis virus</i> (1) ³¹ , <i>Measles virus</i> (2) ^{32,33} , <i>Tick-borne encephalitis virus</i> (1) ³⁴ , <i>Varicella zoster virus</i> (1) ³⁵ , unspecified (9) ³⁶⁻⁴²	14
Cerebral malaria	2	<i>Plasmodium falciparum</i> (1) ⁴³ , unspecified (1) ⁴⁴	1
CNS infection unspecified	3	Unspecified (3) ⁴⁵⁻⁴⁷	0
Respiratory tract infection	10	<i>Influenza</i> (1) ⁴⁸ , <i>Group A Streptococcus</i> (2) ^{49,50} , <i>Mycoplasma</i> (1) ⁵¹ , <i>Klebsiella</i> (1) ⁵² , <i>Epstein Barr Virus</i> (1) ⁵³ , unspecified (4) ⁵⁴⁻⁵⁶	2
HIV-related	22	HIV (20) ⁵⁷⁻⁶⁵ , HIV and <i>John Cunningham (JC) virus</i> (2) ^{66,67}	22 (for HIV)
Syphilis	3	<i>Treponema pallidum</i> (2) ⁶⁸⁻⁷⁰	2
Systemic bacterial infection	31	<i>Coxiella burnetti</i> (1) ⁷¹ , <i>Salmonella typhi</i> (29) ⁷²⁻⁷⁴ , unspecified (2) ^{67,75}	28
Systemic viral infection	4	<i>Cytomegalovirus</i> (2) ^{76,77} , <i>Epstein Barr virus</i> (1) ⁷⁸ , <i>Flavivirus</i> (1) ⁷⁹	3
Prion-related disorders	7	<i>PrP</i> (7) ⁸⁰⁻⁸⁶	7
Other	11	<i>Flavivirus vaccination</i> (1) ⁸⁷ , <i>Tropheryma whipplei</i> (1) ⁸⁸ , <i>E. coli</i> (1) ⁸⁹ , <i>Mycobacterium tuberculosis</i> (1) ⁹⁰ , <i>Taenia solium</i> (1) ⁹¹ , <i>Chlamydia trachomatis</i> (1) ⁹² , <i>Trypanosoma cruzi</i> (1) ⁹³ , unspecified (4) ⁹⁴⁻⁹⁷	2
Total	124		

20% of catatonia has been reported in a systematic review to have a general medical cause, of which CNS inflammation (comprising both infective and immune causes) accounts for 29%.⁹⁸ Numerous infective diseases have been reported to cause catatonia. We present the results of a new systematic search of the literature in Table 1. We identified 124 patients, of whom the majority of cases were published as case reports, with the remaining as case series. Laboratory evidence of infection (such as isolation of the organism in the serum or viral DNA in the cerebrospinal fluid (CSF)) was reported in 85 of the cases (68.5%). A robust temporal association between the infection and

catatonia was reported in 82 of the cases (66.1%). A prior psychiatric disorder was recorded in 16 cases (12.9%) and a prior medical disorder in 26 cases (18.5%), although an absence of a pre-existing condition was often not stated. Only 66 of the cases (53.2%) recorded the presence of at least two features from the Bush-Francis Catatonia Screening Instrument.⁹⁹ In some cases, the catatonia resolved with antimicrobial therapy^{16,17}, whilst in others, it required treatment with benzodiazepines⁵⁹ or electroconvulsive therapy⁷².

It is unclear from the literature how infection can result in catatonia. Possibilities include a direct neurotoxic effect, a psychological reaction to the infection, or mediation by an acute phase response. Interestingly, out of the 47 cases where a specific virus was implicated, 45 of these involved known neurotropic viruses, suggesting a direct neurotoxic effect.¹⁰⁰⁻¹⁰³ Some of the bacterial agents, such as *Borrelia burgdorferi* and *Treponema pallidum* are also known to infect the CNS.

The immunological response also may be important, given that in some neurological disorders, such as meningoencephalitis, damage is caused primarily by the immune reaction.¹⁰⁴ In several cases, an explicit immune response was invoked by the authors to explain the catatonia, such as in paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)⁴⁹, or in *N*-methyl-*D*-aspartate receptor (NMDAR) encephalitis purportedly triggered by yellow fever vaccination⁸⁷, HSV infection^{26,27} or EBV infection²¹. In cases of pyrexia of unknown origin, an infective cause was often assumed, but it is possible that a yet uncharacterised disorder was responsible.^{105 106}

2.2 Depression and inflammation

While cases of overt catatonia in the context of infections are dramatic, the more common neuropsychiatric presentation of infection is a broader phenotype of illness behaviour that resembles depression. This consists of a reduction in motor activity, oral intake, and social interaction⁹, all of which are seen in catatonia. Psychomotor activity may also be slowed in mild experimentally induced infection.¹⁰⁷ This may be due to aberrant activity in parts of the brain involved in interoception and impaired spatial memory performance. Hence the brain's response to inflammation, if severe, could result in a complex movement disorder such as catatonia.^{108,109}

In response to an acute stressor, immune cell trafficking occurs with the movement of leukocytes to, and within, a target organ^{110,111} However, in chronic stress, increased monocyte production and microglial activation result in neuroinflammation and are associated with depressive behaviour.⁹ Depression is often associated with raised levels of pro-inflammatory cytokines, granulocytes, and monocytes.⁹ Regarding subtypes of depression, it is atypical depression, which is characterised by

mood reactivity, hyperphagia, hypersomnia, and the catatonia-like phenomenon of leaden paralysis¹¹², which is most associated with raised inflammatory markers¹¹³. Conversely, psychomotor retardation is more commonly seen in melancholic depression, which is less associated with a peripheral pro-inflammatory state.¹¹³ Seasonal affective disorder (SAD) has also been associated with a pro-inflammatory state, but there has been little research to date on the motor phenotype of SAD.¹¹⁰

2.3 Neuroleptic malignant syndrome and inflammation

Neuroleptic malignant syndrome (NMS) is a neurological emergency precipitated by antipsychotic use and is characterised by muscular rigidity, autonomic dysfunction, and altered consciousness. Patients treated with antipsychotics who have pre-existing catatonia are at an increased risk of developing NMS compared to those who do not have catatonia (3.6% compared to 0.07-1.8%).⁷ Given that there are no clinical features that can reliably distinguish NMS from malignant catatonia,¹¹⁴ some authors consider NMS to be a specific form of antipsychotic-induced malignant catatonia.¹¹⁵ It is common for residual catatonia to remain after the resolution of the full syndrome of NMS.¹¹⁶

There is some suggestion that inflammation may be important to the pathophysiology of NMS, with acute phase responses such as leukocytosis, thrombocytosis, and ferroopenia frequently reported.^{117,118} In two studies, low serum iron emerged as a sensitive biomarker, being present in 32/33 (97%) and 19/20 (95%) of patients^{117,118}. As discussed, the acute phase response can precipitate a depression-like phenotype, but it may also – in combination with antipsychotic medication – cause NMS. Specifically, pro-inflammatory cytokines may reduce the levels of the neuroprotective kynurenic acid, impairing the activity of dopaminergic neurons in the midbrain. The addition of an antipsychotic will likely deplete dopamine further, precipitating NMS.¹¹⁹

It is possible, however, that an inflammatory profile in the blood may be the consequence of rhabdomyolysis, rather than the primary pathology. Anglin and colleagues have disputed this hypothesis on the basis of a case report in which interleukin (IL)-6 and C-reactive protein (CRP) were raised from the beginning of an episode of NMS,^{118,120} but further research is required to ascertain the true direction of causality.

Serotonin syndrome, a rare adverse effect of antidepressant medication, has also been described as a form of drug-induced catatonia,¹ but to date there has been no research linking it to the immune system of which we are aware.¹²¹

2.4 Direct evidence for the acute phase response in catatonia

Table 2: Systematic review of inflammatory markers in catatonia (see box 1 for search criteria)

Laboratory marker	Study	Catatonic subjects	Controls	Results
White cell count	Haouzir et al., 2009 ¹²²	25 patients with acute catatonia	50 non-catatonic patients with similar diagnoses to catatonic patients	No difference in white cell count
	Rao et al., 2011 ¹²³	77 patients with catatonia	None	Responders to lorazepam had a significantly lower monocyte count than non-responders. No difference in other cell counts.
High sensitivity C-reactive protein (hsCRP)	Akanji et al., 2009 ¹²⁴	12 catatonic patients with schizophrenia	87 non-catatonic patients with schizophrenia	hsCRP significantly higher in catatonic patients
Iron	Haouzir et al., 2009 ¹²²	25 patients with acute catatonia	50 non-catatonic patients with similar diagnoses to catatonic patients	Non-significant for lower iron in catatonic patients
	Lee, 1998 ¹²⁵	39 patients with catatonia in psychiatric intensive care units	None	17 patients had iron below reference range
	Peralta et al., 1999 ¹²⁶	40 catatonic patients with psychosis	40 non-catatonic patients with psychosis	Iron significantly lower in catatonic patients

	Carroll & Goforth, 1995 ¹²⁷	12 episodes of catatonia in 11 psychiatric inpatients	None	3 patients demonstrated iron below reference range
	Lakshmana et al., 2009 ¹²⁸	40 catatonic patients	Age- and sex-matched psychiatric patients	No difference in Iron compared to non-catatonic patients
Creatine kinase (CK)	Northoff et al., 1996 ¹²⁹	32 hospital inpatients with catatonia	- 32 non-catatonic dyskinetic psychiatric patients - 32 non-catatonic non-dyskinetic psychiatric patients - 32 healthy controls	CK significantly higher than in healthy controls and non-catatonic non-dyskinetic patients. No difference between catatonic patients and non-catatonic dyskinetic patients.
	Haouzir et al., 2009 ¹²²	25 patients with acute catatonia	50 non-catatonic patients with similar diagnoses to catatonic patients	No difference in CK levels
	Meltzer, 1968 ¹³⁰	2 patients with catatonia	14 patients with non-catatonic psychoses	No difference in CK levels
D-dimer	Haouzir et al., 2009 ¹²²	25 patients with acute catatonia	50 non-catatonic patients with similar diagnoses to catatonic patients	D-dimer significantly higher in catatonic patients

The acute phase response is a core part of the innate immune system. It is initiated by the activation of monocytes and macrophages by a stimulus, such as muscle breakdown, infection, physical injury or psychological stress. In response to these stimuli, cells release pro-inflammatory cytokines such as IL-1, IL-6 and tumour necrosis factor-alpha (TNF- α), which in turn act on receptors throughout the body to promote fever, anorexia, muscle catabolism, and activation of the hypothalamo-adrenal axis. Importantly, they also alter protein synthesis in the liver, causing increased production of acute phase proteins such as CRP, procalcitonin, ferritin, and fibrinogen.^{131,132} Some features of malignant catatonia bear notable similarities to the acute phase response, including fever, motor hypoactivity, and autonomic disturbance.

A summary of the evidence for the presence of systemic inflammation, as measured by acute phase reactants and related proteins, is shown in Table 2. Creatine kinase (CK) is not an acute phase marker, but as it is a marker of muscle breakdown, it is sometimes raised as a downstream consequence of the acute phase response. The evidence for CK elevation in catatonia is equivocal and could be argued to be the result of muscular rigidity and excessive immobilisation rather than indicating a primary muscular pathology. Interestingly, in one study a raised CK predicted a good response to treatment with lorazepam.¹²⁹

One study found the acute phase marker, and fibrin degradation product, D-dimer to be raised in all 25 catatonic patients tested, with a mean value three times higher than in non-catatonic psychiatric patients.¹²² This suggests a plausible mechanism for the increased risk of venous thromboembolism in catatonia but has not yet been replicated.

High sensitivity C-reactive protein (hsCRP) was measured in one study and found to be raised in catatonic patients, but the absolute level of CRP was not very elevated (1.23mg/dL).¹²⁴

Low serum iron was originally hypothesised to be present in catatonia given its similarities to NMS. Ferropeonia is an established feature of the acute phase response and arises due to the upregulated production of ferritin and hepcidin by the liver.¹³³ Two uncontrolled studies have shown that between 25% and 44% of catatonic episodes were accompanied by serum iron levels below the reference range.^{125,127} When catatonic patients have been compared with psychiatric controls, however, the results have been equivocal.^{122,126,128} The authors of one of the negative studies that used unmedicated patients speculated that iron may have been reduced in other reports due to the effect of antipsychotic medications.¹²⁸ Interestingly, in several studies, low serum iron in catatonia has been associated with the subsequent development of NMS.^{125,127,134} Thus, although it is unclear whether iron levels are lower in catatonia in psychiatric controls, it seems that where low serum iron is present in catatonia, there is a risk of an adverse reaction to antipsychotics. This may be because

iron is a cofactor for dopamine synthesis,¹³⁵ so a combination of low iron impairing dopamine production and antipsychotic medications blocking dopamine receptors results in the pathological hypodopaminergic signalling characteristic of NMS.

2.5 Glial dysfunction in catatonia

Abnormalities of cerebral white matter, which is composed of glial cells, have been associated with schizophrenia, depression, and autism.¹³⁶ 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) is a myelin protein that is specific to oligodendrocytes.¹³⁶ In a mouse model, heterozygotes for a *CNP* loss of function genotype showed axonal degeneration and low-grade inflammation, along with a depressive and catatonic phenotype.¹³⁷ Furthermore, this behaviour was alleviated by ablation of microglia, suggesting that microglia-mediated neuroinflammation was underlying the phenotype. When this polymorphism was examined in individuals with schizophrenia, there was a striking association with catatonic-depressive behaviour, a finding that was replicated in an independent cohort.¹³⁸ Mutations of mouse genes encoding two other myelin proteins (myelin basic protein and proteolipid protein) also result in a catatonic phenotype.¹³⁸ How glial dysfunction - both as a result of relevant polymorphisms or other factors - might contribute to the psychomotor features of catatonia clearly represents an important focus of future research.

2.6 Implications of catatonia treatment

The mainstay of current treatment for catatonia is benzodiazepines and ECT, neither of which is classically understood as an immunomodulatory therapy.

Benzodiazepines are positive allosteric modulators at the gamma-aminobutyric acid (GABA)-A receptor. Although research into the function of GABA in the immune system is at an early stage, evidence suggests that GABAergic signalling has a role in suppression of immune responses.¹³⁹ Lymphocytes express GABA-A receptors and activation of these receptors reduces production of pro-inflammatory cytokines.¹³⁹ However, one study specifically in catatonia found higher monocyte counts predicted benzodiazepine non-response.¹²³ Data distinguishing different benzodiazepines are sparse, but some benzodiazepines, such as diazepam and lorazepam (both recognised treatments for catatonia) but not clonazepam, also bind to the translocator protein (TSPO), a mitochondrial protein associated with phagocyte activity, immune cell migration, and cytokine function.^{140,141} In rats, diazepam reduces TSPO in the brain and decreases the number of CNS inflammatory cells, giving it a protective function against experimental autoimmune encephalomyelitis.¹⁴¹ Reports on other GABA-A receptor modulators are limited, but there are epidemiological studies indicating that zolpidem use is associated with higher rates of infections (including of pyelonephritis, which would

be unlikely to be related to respiratory depression), suggesting it may also have an immunosuppressant role.^{142,143}

Regarding ECT, a single session appears to activate the immune system, increasing levels of the cytokines IL-1 β , IL-6, IL-10, and TNF- α . However, a course of several sessions appears to down-regulate immune system activity, at least in animal studies.¹⁴⁴

Minocycline is an antimicrobial that also has anti-inflammatory properties.¹⁴⁵ It has been shown to prevent stress-induced microglial changes in rodents⁹ and has been proposed as an adjunctive treatment for schizophrenia.¹⁴⁶ There is some evidence to suggest that it may reduce negative symptoms in schizophrenia^{147,148}, some of which (such as poverty of speech, affective blunting, and avolition) overlap with catatonia. However, a recent double-blinded, randomised study which specifically aimed to examine the effect of minocycline on negative symptoms did not find any benefit.¹⁴⁹ No studies of which we are aware have investigated minocycline specifically for catatonia, but there is a report of two patients with schizophrenia with prominent catatonic features who responded well to minocycline in the absence of infection.^{150,151}

2.7 The evidence for innate immunity in catatonia

We have argued that psychological stress and infection both result in a release of pro-inflammatory cytokines, which result in a state of motor hypoactivity. In a normal psychomotor response, this may be adaptive, allowing conservation of energy for eliminating a pathogen or avoiding a stressor, and resolving when the stressor ends. However, in depression a prolonged pro-inflammatory state might be maladaptive and cause further dysfunction. In fact, immobilisation itself can also result in activation of the innate immune system.¹⁵²

Studies specifically in catatonia have been sparse and conflicting. An argument could be made that catatonia is an extreme of inflammatory depression, in which the extreme of psychomotor retardation is stupor and mutism, neurovegetative features of catatonia hypothesised to be due to disordered 'top-down' cortico-subcortical signalling.¹⁵³ However, this would not explain the perseverative-compulsive behaviours exhibited in catatonia (posturing, stereotypy, mannerism, echophenomena, and perseveration), which have been proposed to arise due to disrupted cortico-cortical signalling. As Table 1 demonstrates, the infective causes of catatonia are largely pathogens that infect the CNS, which suggests that the causality is mediated by neurotoxic mechanisms, rather than by a systemic inflammatory response, although it is possible that a maladaptive immune response to the pathogen contributes.

3. Autoimmunity

3.1 Autoimmune neurological disorders resembling catatonia

There is a plethora of autoimmune neurological diseases, many of which, such as multiple sclerosis, neuromyotonia and Sydenham's chorea, feature prominent movement disorders. We have chosen the examples of stiff person syndrome (SPS) and narcolepsy to demonstrate some particular points of similarity to catatonia.

SPS is a rare neurological disorder characterised by gradually progressive increased muscle tone with the preservation of muscle power, sensation, and cognitive function. The majority of patients have autoantibodies against the enzyme glutamic acid decarboxylase (GAD), although some have antibodies against GABA-A receptor associated protein, which is present in the postsynaptic terminals of GABA synapses.¹⁵⁴ GAD is an enzyme that converts glutamate to GABA; however, the pathogenicity of GAD autoantibodies is unclear since GAD is an intracellular antigen and neuronally binding autoantibodies would not normally be expected to cause dysfunction of their target protein *in vivo*. It is plausible that either the autoantibodies are internalised, or that a GAD epitope is presented on the cell surface during exocytosis.^{155,156} Others have proposed that SPS is primarily a T-cell-mediated disorder and the GAD antibodies arise secondarily.¹⁰⁴

SPS bears several similarities to catatonia and one author has suggested testing for GAD autoantibodies to distinguish between them.⁷ In addition to the immobility, an emotionless facial expression is often present in SPS, similar to the flat affect often seen in catatonia. Furthermore, SPS is strongly associated with anxiety, which may be secondary to the motor abnormalities and fear of falling but has also been postulated to be more central to the disorder, given that GABA receptor hypofunction results in rigidity and anxiety. Moreover, hypertonic episodes in SPS can have psychological triggers.¹⁵⁴ As with catatonia, the mainstay of treatment for SPS is benzodiazepines; however, immunotherapy in the form of intravenous immunoglobulin, corticosteroids and the anti-B-cell monoclonal antibody rituximab are increasingly used. The SPS variant, progressive encephalomyelitis with rigidity and myoclonus, responds dramatically to immunosuppression.^{154,155}

Narcolepsy type 1 is a sleep disorder that arises due to depletion of the orexin-producing neurons in the hypothalamus. Evidence that this is immune-mediated comes from the linkage to HLA-DQB1*06:02 as well as outbreaks coinciding with epidemics of, and vaccination to, the H1N1 influenza virus, suggesting a possible role for molecular mimicry between epitopes of the influenza virus and the disease-relevant proteins such as the orexin receptor.¹⁵⁷ Recently, a small study has suggested that some patients with narcolepsy have autoantibodies to the NMDA receptor, without the seizures or autonomic disturbance characteristic of NMDAR autoimmune encephalitis.¹⁵⁸

Narcolepsy type 1 also features cataplexy, a sudden loss of motor tone usually triggered by positive emotions. This usually lasts for up to two minutes, but occasionally status cataplecticus lasting for hours to days can occur,¹⁵⁹. This has been hypothesised to be due to either a prolonged emotional response to the original stimulus, or an emotional response to the cataplexy *per se*. A comparison between cataplexy and catatonia is shown in Table 3, illustrating the dramatic psychomotor phenotype that may result from a CNS autoimmune process.

Table 3: Comparison of catatonia and cataplexy (in the context of narcolepsy)

	Catatonia	Cataplexy
Trigger	Strong negative emotions	Strong positive emotions
Tone	Increased with posturing, but preservation of respiratory muscles	Atonic with preservation of respiratory muscles
Awareness	Retained	Retained
Main associated psychiatric disorders	Depression, psychosis	Depression, social anxiety
Pharmacological treatment	GABA-A agonists	Antidepressants, sodium oxybate (GABA-B agonist)
Duration	Days-weeks	Up to 2 minutes (longer in status cataplecticus)

3.2 Autoimmune disorders causing catatonia

Table 4: Systematic review of autoimmune causes of catatonia (see box 1 for search criteria)

Category of autoimmunity	<i>n</i>	Specific disorder	<i>n</i>
Autoimmune thyroid disorders	13	Hyperthyroid state ¹⁶⁰⁻¹⁶²	3
		Hypothyroid state ¹⁶³⁻¹⁶⁵	4
		Euthyroid state with thyroid antibodies ¹⁶⁶⁻¹⁶⁹	4
		Thyroid state not stated ^{170,171}	2
Autoimmune encephalitis	259	GABA-AR encephalitis ^{172,173}	2
		NMDAR encephalitis ^{27,158,170,174-259}	249
		Progressive encephalomyelitis with rigidity and myoclonus (PERM) ²⁶⁰	1
		'Voltage-gated potassium channel (VGKC) complex' encephalitis ²⁶¹⁻²⁶³	4

		Unspecified ^{51,264}	3
Demyelinating disorders	13	Acute disseminated encephalomyelitis ^{265,266}	2
		Multiple sclerosis ²⁶⁷⁻²⁷⁶	10
		Neuromyelitis optica ²⁷⁷	1
Pernicious anaemia	4	Pernicious anaemia ²⁷⁸⁻²⁸¹	4
Systemic lupus erythematosus (SLE) and related	53	Antiphospholipid syndrome ^{282,283}	2
		SLE ^{170,174,284-316}	51
Other	4	Addison's disease ³¹⁷	1
		Crohn's disease ³¹⁸	1
		MOG antibody disease ³¹⁹	1
		Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) ⁴⁹	1
Total	346		

Autoimmune disorders causing catatonia are shown in Table 4 as the results of a systematic search of the literature. The majority are represented by case reports and case series, although there are some larger case series for NMDAR encephalitis, as shown in Table 6. 224 of the cases (65.1%) recorded at least two features from the Bush-Francis Catatonia Screening Instrument. ⁹⁹ 18 patients (5.2%) recorded a prior psychiatric disorder and 33 (9.6%) a prior medical disorder, although an absence of a pre-existing condition was often not stated. In the vast majority, the autoimmune disorder appeared to be the proximal cause of the catatonia. In a few, the autoimmune disorder was a more distal cause, as in one case where a patient with autoimmune polyendocrine syndrome developed autoimmune destruction of the adrenal gland (Addison's disease), resulting in hyponatraemia and subsequent extrapontine myelinosis, the latter precipitating catatonia. ³¹⁷

In addition, it is notable that the 22q11.2 deletion syndrome, which features thymic aplasia and a resultant absence of peripheral T-cells, ³²⁰ has also been linked to catatonia. ³²¹ Whether this association is due to immunodeficiency, the high rates of various autoimmune disorders present in the syndrome, or to another cause remains unclear.

The most noteworthy result from Table 5 is that 72.0% of all cases of autoimmune catatonia reported are due to NMDAR encephalitis, despite the fact that the disorder was only described in

2007.³²² Before discussing this finding of autoimmunity directed against the CNS in depth, we will illustrate the complexity of autoimmune catatonia with three examples of peripheral autoimmunity.

Pernicious anaemia is due to vitamin B12 deficiency secondary to autoimmune destruction of the gastric parietal cells.³²³ In addition to the well-known features of impaired proprioception, depression, and dementia, two cases of catatonia associated with pernicious anaemia have been reported.^{278,280} In one, an inverse relationship between vitamin B12 levels and catatonic symptoms was observed.²⁷⁸ Given that these patients responded to vitamin B12 supplementation and catatonia has also been reported in vitamin B12 deficiency due to dietary insufficiency without evidence of autoimmunity,^{324,325} we may surmise that vitamin B12 acts as a mediator between pernicious anaemia and catatonia.

The situation is less straightforward in thyroid disease. The issue is of historical interest, as Gjessing's research found that supplementation with thyroid hormone could successfully treat recurrences of periodic catatonia.³²⁶ Catatonia has been reported in patients with thyroid autoantibodies with hyperthyroid¹⁶⁰⁻¹⁶², hypothyroid^{163,164} and euthyroid^{166,167} states. However, catatonia has also occurred in hypothyroidism due to thyroidectomy³²⁷, so it is unclear whether thyroid status, the presence of the autoantibodies, or both is the causally relevant factor.

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disorder. Neuropsychiatric symptoms of SLE are well recognised and have a lifetime prevalence of at least 80%.²⁹⁴ The presence of antibodies against the NR2 subunit of the glutamate NMDA receptor and anti-ribosomal P antibodies have been linked to psychosis in this patient group.³²⁸ 51 cases of catatonia in SLE have been recorded, in some of whom it was the presenting feature. Successful treatment consisted of immunosuppressant therapy for SLE, as well as benzodiazepines or electroconvulsive therapy for the catatonia.^{300,313} In terms of immunological profile, these patients tended to have high titres of antinuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA); however, it is hard to make further comparisons because testing panels have varied across studies.

One group has reported 84 cases of paediatric catatonia of which they suspected 7 had an autoimmune origin, including two patients with evidence of inflammation who were responsive to immunosuppression but who could not be diagnosed with any known disorder.¹⁷⁴

3.3 Autoimmune disorders directed at CNS targets causing catatonia

Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) and the broader concept of paediatric acute-onset neuropsychiatric syndrome (PANS) are characterised by an abrupt onset of obsessive behaviours or motor tics.³²⁹ This may be due to

molecular mimicry, whereby antigens on the infective agent bear a similarity to and provoke a host immune response to self CNS antigens.³³⁰ Antistreptococcal antibodies are often positive,³³¹ although results of immunotherapy have been equivocal.³³² There has been one reported case of a boy who developed catatonic symptoms in addition to obsessionality following infection with group A Streptococcus; he responded well to lorazepam and plasmapheresis.⁴⁹

Autoimmune encephalopathies, as examples of autoimmune disorders directed at CNS targets, merit special consideration. T-cell mediated disorders, such as acute demyelinating encephalomyelitis can occasionally present with catatonia.²⁶⁵ However, catatonia is more commonly a feature of autoimmune encephalitides associated with antineuronal antibodies. These antibodies can cause internalisation of the antigen, inhibiting its function.¹⁰⁴

Given the centrality of benzodiazepines in treatment for catatonia, it is unsurprising that catatonia has been reported in two patients with GABA-AR antibodies.^{173,333} It is possible that catatonia may be more common, as there has not hitherto been careful psychiatric phenotyping among this population.³³⁴ Interestingly, in one of the patients reported with catatonia, GABA-AR antibodies were present in the serum on the original presentation, but not in the context of relapse, highlighting the risk of testing on a single occasion in missing a clinically significant syndrome.³³³

NMDAR encephalitis is increasingly considered as an organic cause of psychosis, although there is controversy as to whether this is merely in the context of classical encephalitis or in 'isolated psychiatric' presentations also.^{8,335} In fact the association with catatonia seems to be even stronger than the association with psychosis.²⁵⁹ Where catatonia is reported, it is often malignant catatonia and tends to co-occur with psychosis³³⁶ and mania³³⁷. NMDAR encephalitis is strongly linked to NMS, with one study suggesting as many as 21 out of 36 (58%) patients with NMDAR antibody encephalitis who were administered antipsychotics developed suspected NMS.³³⁸ Table 6 summarises the case series in which the authors have specified whether catatonia was present. The range of catatonic features reported is wide and includes echolalia, grimacing, posturing and alternating hypermotor and hypomotor activity.²⁵⁹

Table 6: Rates of catatonia (as identified by authors) in case series of NMDAR encephalitis

Study	Participants	Cases of catatonia	%
Dalmau et al., 2008 ²⁵⁹	100	88	88.0
Tsutsui et al., 2012 ¹⁵⁸	3	2	66.7
DeSena et al., 2014 ^{226 a}	8	5	62.5
Kruse et al., 2015 ²²⁴	12	9	75.0

Duan et al., 2016 ¹⁷⁵	28	19	67.9
Granata et al., 2018 ^{177 a}	18	8	44.4
Herken and Prüss, 2017 ^{184 b}	53	10	18.9
TOTAL	222	141	63.5

^a All paediatric cases; ^b Relied on retrospective analysis of charts, so likely underestimated rates of catatonia

A few studies have examined comparative rates of NMDAR autoantibody positivity among different diagnostic groups. Of 459 psychiatric patients, two had IgG antibodies against NR1a in serum and CSF; both had catatonia and were ultimately reclassified as NMDAR encephalitis. ³³⁹ Among 49 psychiatric inpatients with serum antineuronal antibodies, 9 of the 13 patients with NMDAR antibodies had catatonia, compared to only 3 of the remaining patients. ²²⁴ Another study found higher NMDAR positivity among patients with catatonia, compared to a control group of healthy volunteers (although controls were younger than the patients and the investigators used an unusual continuous measure of anti-NMDAR immunofluorescence). ³⁴⁰ One study examined Bush-Francis Catatonia Rating Scale scores in patients with first episode psychosis and found that catatonic features were actually less common in patients with antineuronal antibodies. ³⁴¹ Recent work from our group with individuals at ultra-high risk of psychosis suggests more severe catatonic features in individuals with NMDAR antibodies. ³⁴²

NMDAR encephalitis has only been described in the last decade but has led to a re-evaluation of encephalitis lethargica ³⁴³, first recognised in 1917, due to notable similarities. ³⁴⁴ Encephalitis lethargica is characterised by profound sleep impairment (insomnia, hypersomnia or sleep inversion), extrapyramidal movement deficits, and neuropsychiatric symptoms. ¹² Although historically linked to the 1918 influenza pandemic, the evidence for a causal association is sparse. ¹² More recently, investigations have found high rates of antibodies to the NMDAR and the dopamine D2 receptor in the serum of children with encephalitis lethargica, raising the intriguing prospect that many patients exhibiting catatonia previously diagnosed with the disorder, may actually have been suffering from antibody-mediated encephalitis. ^{345,346}

3.4 A model for autoimmunity in catatonia

When we considered the role of the innate immune system, we considered the possibility that inflammation itself was responsible for the stuporous aspects of catatonia. As far as adaptive immunity is concerned, the specificity of the antigen may be the most important determinant of the resulting neuropsychiatric phenotype, including catatonia. There is then an effect downstream from the immune activation, dependent on the antigen targeted. Autoimmune neurological disorders present differently depending on the target for autoantibodies or T-cells; frequently these are

neurotransmitter receptors with ensuing downstream effects on receptor dysfunction. In autoimmune encephalitis, the presentation depends on the specific antibodies present.³⁴⁷ In the specific case of NMDAR encephalitis, there is often little evidence of complement activation and neuronal degeneration.³⁴⁸ The fact that ketamine and phencyclidine – both NMDAR antagonists – cause catatonia^{349,350} suggests that it is NMDAR antagonism that is responsible, the implication being that NMDAR antibody encephalitis is more usefully understood as a synaptopathy. Genetic hypofunction of the NMDAR due to GRIN1 mutation also appears to predispose to psychosis.³⁵¹ Similarly, benzodiazepine withdrawal presents similarly to GABA-AR encephalitis.^{352,353}

Autoimmunity, therefore, appears to cause catatonia primarily by specific action against central or peripheral antigens. It is possible, however, that there may be some secondary inflammation, which may perpetuate a phenotype-relevant immune response.

3.5 A model for glutamatergic hypofunction in catatonia

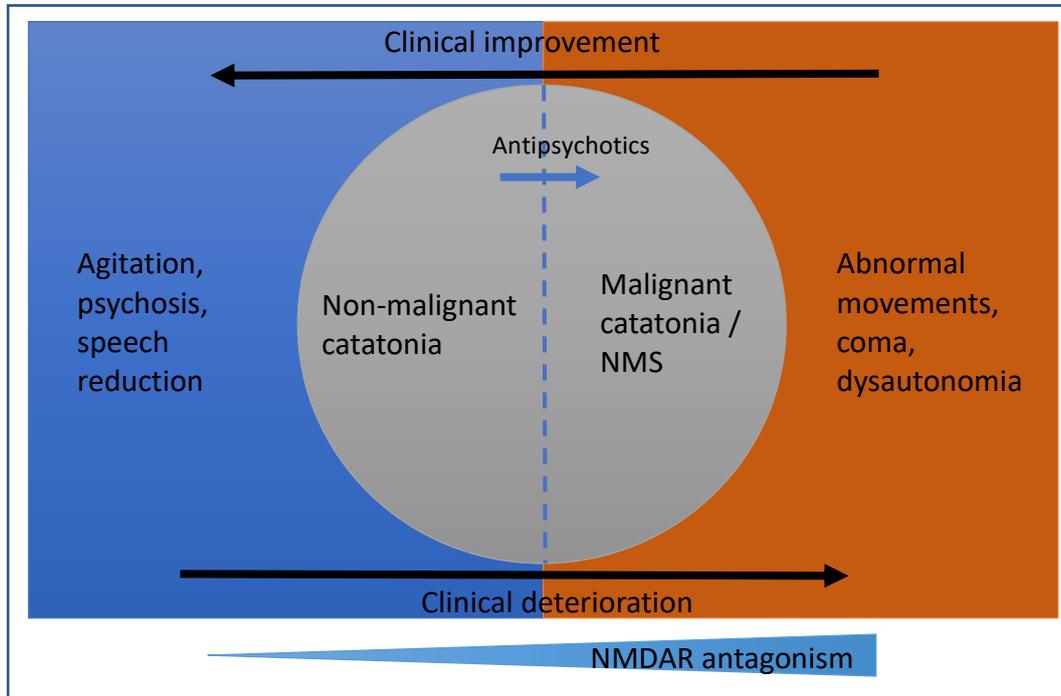
The close association between NMDAR encephalitis and catatonia may provide valuable insight into the pathophysiology of catatonia. NMDAR encephalitis causes internalisation of the NMDAR, resulting in a reversible reduction in the number of receptors and impaired AMPAR-mediated long-term potentiation.^{354,355} This is consistent with catatonia also resulting from use of the recreational noncompetitive NMDA antagonists, ketamine and phencyclidine.^{349,350}

To integrate findings of effective treatment with GABA-A receptor agonists and NMDAR antagonists, Northoff has proposed a model of catatonia in which the normal inhibition of excitatory glutamatergic cortico-cortical association fibres by GABAergic neurons in the orbitofrontal region is impaired.¹⁵³ In mice, the NMDAR antagonist MK-801 shows a bimodal effect on grooming and rearing behaviour: at low doses this behaviour is suppressed, but as the dose increases, behaviour normalises, before being suppressed again at higher doses.^{356,357} This may explain why catatonia is characterised, not only by immobility, but occasionally by ‘catatonic excitement’. An explanation for this finding may rely on the fact that the NMDAR is expressed by excitatory glutamatergic neurons and by inhibitory GABAergic neurons.³⁵⁸ Moreover, both reduced and excessive NMDAR activity can result in neuronal apoptosis³⁵⁹, but at physiological levels it can promote neuronal survival.³⁶⁰

Dalmau and colleagues have proposed a model for anti-NMDAR encephalitis, in which increasing NMDAR blockade results initially in behavioural and psychotic symptoms, and at higher antibody titres, by neurological and autonomic dysfunction.³⁴³ One hypothesis would be that catatonia occupies the ground between these two states (Figure 1). Pharmacological or antibody-mediated

NMDAR hypofunction may cause catatonia, as well as resulting in progression to malignant catatonia.

Figure 1: A model for glutamatergic hypofunction in catatonia



4. Conclusion

Catatonia is a disorder that is heterogeneous in presentation and aetiology. However, its generally favourable response to treatment with benzodiazepines or electroconvulsive therapy suggests a common pathophysiology. Activation of the innate immune system can lead to the neurovegetative features of catatonia, but the evidence for the acute phase response in catatonia is preliminary and sometimes conflicting. There is, moreover, the question of whether any peripheral inflammation in catatonia arises secondary to immobility and muscle breakdown. Examining the relationship of catatonia to the adaptive immune system reveals a strong and specific association with NMDAR encephalitis, which can cause the full range of catatonic features. This suggests that adaptive immunity may cause catatonia through action at specific extracellular antigens, rather than immune activation *per se*. Additionally, it illustrates the importance of glutamatergic function in catatonia. It is possible that as more autoimmune disorders are characterised, more cases of catatonia will be explained in this way.

Although we have considered the innate and adaptive immune systems separately, in reality they are deeply interconnected. For instance, NMDAR encephalitis (a disorder of the adaptive immune system) entails a very high risk of NMS (a disorder with prominent activation of the innate immune system). Malignant catatonia remains an enigmatic entity and it is possible that it could be accounted for by autoimmune disorders such as NMDAR encephalitis.

Table 7: Questions for future research

Domain	Questions to be addressed
Epidemiology	<ul style="list-style-type: none"> • Is catatonia overrepresented in individuals with autoimmune disorders? • What are the rates of catatonia in GABA-AR encephalitis when systematic detection methods are used?
Laboratory investigations	<ul style="list-style-type: none"> • In studies of depression, is there evidence that raised inflammatory markers are associated with catatonic features? • Are there relapsing and remitting inflammatory markers in periodic catatonia? • Are the rates of antibodies to NMDAR, GABA-AR, GAD and other encephalitis-associated antibodies elevated in patients with catatonia? • Will larger genetic studies of catatonia show linkage to HLA or other immune-specific regions? • Do inflammatory markers predictors response to ECT?
Neuroimaging	<ul style="list-style-type: none"> • Is there a reduced density on single photon emission computed tomography (SPECT) or positron emission tomography (PET) studies of NMDA receptors in catatonia? • Will the use of specific ligands reveal CNS immune cell (e.g. microglia or astrocyte) activation in catatonia?
Therapy	<ul style="list-style-type: none"> • Is immunomodulatory therapy (such as corticosteroids, plasmapheresis or rituximab) an appropriate treatment option in catatonia? • Is minocycline an effective treatment for catatonia? • Is immunosuppressant therapy effective for NMS?

Finally, is it possible to conclude whether catatonia is due to activation of the immune system? In many cases, there is little compelling evidence for this. However, where infection or autoimmunity are directed at specific targets in the CNS or periphery, there is a high risk of catatonia. Further investigations based on this concept (Table 7) may assist in elucidating the pathophysiology and improving the treatment of catatonia.

Search Strategy and Selection Criteria

We searched PubMed for articles published from inception to Sept 31, 2018 with the terms “catatoni*” in association with any of the following terms: “immune*”, “autoimmun*”, “inflamm*”, “T-cell”, “B-cell”, “glia*”, “microglia*”, “acute phase”, “innate”, “adaptive”, “encephalitis”, “antibod*”, “infect*”, “interleukin”, “cytokine”, “monocyte”, “macrophage”, “leukocyte”, “lymphocyte”, “granulocyte”, “phagocyte”, “TNF”, “C-reactive protein”, “dendritic cell” and “immunoglobulin”.

This primary search along with the references of selected review articles revealed 3 areas that were suitable for systematic summaries of the literature, namely infective causes of catatonia, autoimmune causes of catatonia and inflammatory markers in catatonia. To conduct these, we searched 6 databases (AMED, BNI, CNINAHL, EMBASE, Medline, PsycINFO and PubMed) for catatonia and MESH terms (or equivalent) in conjunction with relevant specific search terms (e.g. “infect*”, “virus”, “bacteria” etc). After de-duplication, articles were screened on titles and abstracts before relevant full text articles were reviewed by the first author and systematically included in tables in the manuscript. Only articles with full texts or sufficiently detailed abstracts in English were included.

Author Contributions

The manuscript was planned by JPR, TAP, GB and ASD. JR conducted a literature search and drafted the manuscript. TAP, GB and ASD reviewed the manuscripts, made amendments to it and added further references. All authors have approved the final manuscript.

Declaration of Interests

The authors report no conflicts of interest.

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