University College London Division of Psychiatry

Epidemiology and Neuropsychiatry of Catatonia

A thesis submitted for the degree of Doctor of Philosophy (PhD)

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July 2023

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Subsidiary Supervisors: Professor Anthony S David & Dr Michael S Zandi

Thesis Committee: As above in addition to Professor Angela Vincent & Professor Mitul A Mehta

Funding: Wellcome Trust

Declaration

I, Jonathan P Rogers, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

1.1 Background

Catatonia is a severe form of psychomotor disturbance associated with a range of general medical and psychiatric disorders. After almost 150 years, most of the existing literature relies on case reports and series. This has resulted in gaps in the epidemiology and neuropsychiatry of this condition.

1.2 Aims

In this thesis, I aim to characterise the epidemiology, neuroimmunology, structural neuroimaging findings and EEG findings in catatonia.

1.3 Methods

I conducted a narrative review of studies related to the immunological findings in catatonia and related conditions, informed by several systematic literature searches. I used anonymised electronic healthcare records from South London to further examine the epidemiology, inflammatory markers and neuroimaging of catatonia. Inpatients with catatonia were compared to inpatients without catatonia. To characterise the EEG findings, I conducted a systematic review and bivariate meta-analysis to determine its diagnostic test accuracy in determining the aetiology of catatonia.

1.4 Results

A literature review found that various viral, bacterial and parasitic infections have occasionally been reported in association with catatonia. The most commonly reported form of autoimmune catatonia is NMDAR encephalitis. Using electronic healthcare records, I found that the incidence of catatonia was approximately 1 per 10,000 person-years. Serum NMDAR antibodies were more common in patients with catatonia than in a psychiatric comparison group, but other inflammatory markers were not comparably increased. Abnormalities on structural MRI scans occurred in 34% of patients with catatonia, but there was no difference in adjusted comparisons to other psychiatric patients. Neurological and other general medical conditions in the literature were usually found to be distinguishable from psychiatric catatonia using clinical electroencephalography.

1.5 Conclusions

Catatonia remains an important problem in clinical and academic neuropsychiatry. There is promise for neuroimmunological and electroencephalographic biomarkers. Future research requires prospective design, relevant comparison groups and identification of more homogeneous subgroups.

Impact statement

Regarding academic impact, the studies contributing to this thesis have been published in *The Lancet Psychiatry*, *Psychological Medicine*, *The Journal of Neuropsychiatry and Clinical Neurosciences* and *EClinicalMedicine*. My work in defining a cohort of patients with catatonia in electronic healthcare records for this thesis has also been a springboard for several other papers using this dataset, examining the psychopathology of catatonia, the seasonality of catatonia, catatonia in the peripartum period and catatonia related to substance use. (Dawkins et al., 2022; Delvi et al., 2023; Mastellari et al., 2023; Yeoh et al., 2022) In addition, the current work has formed the background and rationale for an ongoing prospective study of catatonia that I am conducting.

In methodological terms, I have been able to highlight how existing studies of catatonia have had limitations in terms of their sample sizes and in lacking comparison groups. In response to this, I have brought some novel techniques to the catatonia field, including the use of large-scale electronic healthcare records and the use of multiple imputation to address problems with missing data. I have also been able to highlight for future researchers the lines of investigation that are likely to be more or less productive in the study of catatonia.

In terms of clinical impact, work on this PhD has equipped me with clinical expertise in catatonia. I am regularly consulted for specialist clinical advice about patients around the country and I have given talks on the subject for psychiatrists, neurologists and cognitive neuroscientists in settings ranging from local hospital teaching to national and international conferences. I think the most important message from my thesis for practising clinicians is that catatonia has not disappeared and is still a major clinical issue. This and other evidence from my thesis has contributed to the evidence base behind the new British Association for Psychopharmacology Catatonia Guidelines. (Rogers et al., 2023) To extend my reach to clinicians further, I have created YouTube videos about catatonia, one of which has been viewed over 70,000 times.

In terms of impact on the public, one article I wrote for *The Conversation* about catatonia, a website that hosts articles written by academics, has attracted more than 100,000 readers. (Rogers, 2022) I have also appeared on the BBC World Service to discuss the related condition of encephalitis lethargica and have been interviewed by the Swiss-German newspaper of record, the *Neue Zürcher Zeitung*, for a feature on catatonia. I have created a website hosted by the UCL Institute of Mental Health, which provides education about catatonia (https://www.ucl.ac.uk/mental-health/catatonia). It has received more than 4000 visitors and is recommended in a patient leaflet produced by the Royal College of Psychiatrists.

Finally, more broadly, I have used the knowledge I have acquired in the field of immunopsychiatry in extensive media contributions on the neuropsychiatric sequelae of COVID-19. The aggregate of this work led

to me being awarded the British Association for Psychopharmacology's Senior Public Communication Prize in 2021.

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   JPR, TAP and ASD designed the project. MP, MB and AK conducted data extraction with advice from RS and RP. JPR, NB, AG and JK manually reviewed the patient records. JPR conducted the statistical analysis with support from BC and GL. JPR drafted the manuscript with specialist advice from TAP, AB, AA, MSZ, RS, GL and TRN. All authors reviewed and approved the final manuscript.

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JPR conceived and designed the project, supported by ASD, MAM and TAP. MP, AJ and AK extracted the data. RJ and RT coded the MRI scan findings with support from JPR. JPR conducted the analysis, supported by FS and GL. RJ and RT wrote a first draft of the manuscript, which was then revised by JPR. MAM, FS, TAP, TRN, AA, AH, GL, MSZ and ASD supported with the interpretation of the data. All authors contributed to the writing of the manuscript and approved it. JPR takes overall responsibility for the data.

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Acknowledgements

I am greatly indebted to my supervisors, Glyn Lewis, Anthony David and Michael Zandi, who have generously provided support and advice over several years. I have been extremely grateful for their kindness, wisdom and persistence. The support of my wider thesis committee from Angela Vincent and Mitul Mehta has been massively appreciated.

I would also like to thank my funder, the Wellcome Trust, my upgrade examiner, Valeria Mondelli, and the patients whose data enabled this project.

In addition, almost all the work presented in this thesis has been highly collaborative and would not have been possible without the support of a large number of individuals who worked with me on various papers: Ali Amad, Nazifa Begum, Graham Blackman, Adrian Bomford, Matthew Broadbent, Ben Carter, Benjamin Cross, Anthony David, Karrish Devan, Jack Fanshawe, Charles Fry, Dory Ghanem, Anna Griffin, Alexandre Haroche, Paris Hosseini, Amelia Jewell, Roshell Jeyaventhan, Jessie Ke, Anna Kolliakou, Glyn Lewis, Tomas Mastellari, Mitul Mehta, Puja Mehta, Timothy Nicholson, Dominic Oliver, Rashmi Patel, Thomas Pollak, Megan Pritchard, Aman Saini, Francesca Solmi, Biba Stanton, Robert Stewart, Ramya Thanikasalam, Apoorva Vijay, Umesh Vivekananda, Rebecca Whincup and Michael Zandi. Particular mention should go to Tom Pollak, who provided the seed for many of the ideas developed in this thesis.

Soli Deo gloria.

Abbreviations

ADEM – acute demyelinating encephalomyelitis

AMPA(R) – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (receptor)

AUC – area under the ROC curve

BFCRS – Bush-Francis Catatonia Rating Scale

BFCSI – Bush-Francis Catatonia Screening Instrument

CASPR2 – contactin-associated protein-like 2

CI – confidence interval

CK – creatine kinase

CNS – central nervous system

CRP – C-reactive protein

CT – computed tomography

DSM – *The Diagnostic and Statistical Manual of Mental Disorders*

ECT – electroconvulsive therapy

EEG – electroencephalogram

FDG-PET – fluorodeoxyglucose-positron emission tomography

FTE – full-time equivalent

GABA – γ-aminobutyric acid

GAD – glutamic acid decarboxylase

GMC – general medical condition

HIV – human immunodeficiency virus

HoNOS – Health of the Nation Outcome Scales

HSV – herpes simplex virus

ICD – International Classification…

ICU – intensive care unit

IPD – individual participant data

IQR – interquartile range

LGI1 – leucine-rich glioma-inactivated 1

MAR – missing at random

MCAR – missing completely at random

MLR – monocyte/lymphocyte ratio

MNAR – missing not at random

MRI – magnetic resonance imaging

NCRS – Northoff Catatonia Rating Scale

NHS – National Health Service

NLP – natural language processing

NLR – neutrophil/lymphocyte ratio

NMDA(R) – *N*-methyl-D-aspartate (receptor)

NOS – not otherwise specified

OR – odds ratio

PANS – paediatric autoimmune neuropsychiatric syndrome

PERM – progressive encephalomyelitis with rigidity and myoclonus

PLR – platelet/lymphocyte ratio

ROC – receiver operating characteristic

SD – standard deviation

SLE – systemic lupus erythematosus

SPS – stiff person syndrome

SROC – summary receiver operating characteristic

UCL – University College London

UK – United Kingdom

USA – United States of America

VGCC – voltage-gated calcium channel

VGKC – voltage-gated potassium channel

1 Scope of thesis

This PhD is conducted as part of a Wellcome Trust Clinical Training Fellowship at UCL.

The PhD is focussed around one particular neuropsychiatric disorder: catatonia. The overall aim is to characterise the neuroimmunology, epidemiology, structural neuroimaging findings and EEG findings of this disorder, using a range of methods.

In Chapter 2 of this report, I give some background to this research by considering the definition of catatonia as a distinct neuropsychiatric disorder, before considering the state of knowledge about catatonia in terms of its neuroimmunology, epidemiology, structural neuroimaging and EEG findings. I conclude this chapter by stating the limitations of our current understanding in these areas and justifying the important outstanding questions.

In Chapter 3, I use a narrative review, informed by systematic searches of the literature, to examine the evidence linking catatonia to the function or dysfunction of the immune system. I have dedicated an entire chapter to review this evidence because it is a relatively novel idea and has not been considered in depth before. In contrast, reviews covering the epidemiology and neuroimaging of catatonia have been written in the past, (Haroche et al., 2020; Solmi et al., 2018) while my coverage of EEG findings is a literature review in itself.

In Chapters 4 and 5, I present studies using electronic healthcare records to examine catatonia in a large dataset. Comparison is made to psychiatric patients without catatonia. Chapter 4 examines epidemiology and inflammatory markers, while Chapter 5 examines structural neuroimaging findings from clinical MRI scans.

In Chapter 6, I conduct a systematic review of EEG findings in catatonia, performing a meta-analysis to establish the diagnostic test accuracy of this modality in determining the aetiology of catatonia.

Each chapter considers the implications of its own results. To conclude the thesis, in Chapter 7 I examine the messages from the thesis as a whole. I draw out the limitations that are widely applicable and examine what implications this programme of research has for clinical and academic practice.

2 Introduction

Part of this chapter has previously been published in The Maudsley Practice Guidelines for Physical Health Conditions in Psychiatry. (Taylor et al., 2020)

2.1 Summary

Catatonia is a severe form of psychomotor disturbance associated with a range of general medical and psychiatric disorders. Despite its heterogeneous presentation, there are arguments to study it as a single entity, given that its different presentations are highly comorbid and it responds to specific treatments. After almost 150 years of research, most of the existing literature still relies on case reports and case series. This has resulted in difficulties in understanding the epidemiology of catatonia with basic questions such as its incidence, prevalence, longitudinal course, demographics and mortality remaining uncertain. Although catatonia has occasionally been linked to infectious diseases, it is only more recently that findings suggesting an association with autoimmune conditions have been reported. These raise the possibility that the immune system may play a role in the aetiopathogenesis of catatonia; however, the rather disparate findings in this area have yet to be synthesised. A similar phenomenon has occurred in electroencephalographic investigations of catatonia, where many small studies and a few large studies have been performed, but the literature has not been adequately amalgamated to establish whether the technique has any value in clinical practice. The neuroimaging literature in catatonia has been synthesised, but the preponderance of small studies and the frequent lack of control groups without catatonia mean that reporting bias is likely to be substantial and the clinical relevance of findings is unclear. In this thesis, I aim to better characterise the epidemiology, neuroimmunology, electroencephalography and structural neuroimaging of catatonia.

2.2 Definition and historical status of catatonia

Catatonia is a severe form of psychomotor disturbance with a heterogeneous presentation. It has been claimed to affect approximately 10% of acute psychiatric inpatients and is frequently under-recognised. (Solmi et al., 2018; van der Heijden et al., 2005) It is associated with a range of underlying disorders and various medical complications. In this introduction, I present the current understanding of catatonia and highlight outstanding questions for future research.

The 19th century saw increasing interest in a range of movement disorders in psychiatry and neurology. A major controversy existed over their nosological status as either the result of direct agency or unconscious 'reflexive' activities. Griesinger endeavoured to resolve this controversy in the middle of the 19th century by positing that agency was responsible for some movement disorders and unconscious processes for others. (Berrios and Marková, 2018)

Karl Ludwig Kahlbaum's description of catatonia in 1874 as a motor disorder in the context of mental illness challenged this dichotomy. (Kahlbaum, 1874) Kahlbaum described an early phase of alternation between agitation and stupor with a later phase exhibiting more qualitative motor signs. (Kendler, 2019) This paved the way for a broader consideration of motor disorders in psychiatry with Wernicke's concept of *Motilitätpsychosen* (motility psychoses). (Wernicke, 1906)

Over the course of the 20th century, catatonia became subsumed into the Kraepelinian concept of *dementia praecox* and subsequently schizophrenia. (Shorter and Fink, 2018) While this classification and its subsequent adoption into American and international diagnostic manuals facilitated a reproducible algorithm for the diagnosis of catatonia, it neglected the possibility that catatonia might exist outside of a diagnosis of schizophrenia. In a seminal paper, Gelenberg argued that – rather than being a subtype of schizophrenia – catatonia exists as a syndrome with diverse possible aetiologies, ranging from affective disorders, focal brain lesions, metabolic conditions and pharmacological agents. (Gelenberg, 1976) He conceived it as 'a cluster of signs and symptoms frequently appearing together', such features including motor signs, psychosocial withdrawal, excitement and repetitive behaviour. In the same year, Abrams and Taylor examined 55 patients in psychiatric units with at least one catatonic sign, finding that only 4 met criteria for schizophrenia, while the majority had an affective disorder. (Abrams and Taylor, 1976)

It took until the publication of DSM-IV in 1994 to recognise catatonia as a specifier in mood disorders and general medical conditions, while DSM-5 added a category of *Catatonic disorder not otherwise specified*. (American Psychiatric Association, 2013; Tandon et al., 2013) ICD-11 has taken one step further and has created an entire separate diagnostic category for catatonia, permitting a diagnosis in the context of other psychiatric disorders, substance use and general medical conditions, as well as an unspecified category. (World Health Organization, 2018)

Other major developments in catatonia have included Stauder's description of *tödliche Katatonie* (lethal catatonia), (Stauder, 1934) which is now more accurately termed *malignant catatonia*. The development of electroconvulsive therapy (ECT) opened up the prospect of effective therapy. (Bini and Cerletti, 1938) Barbiturates were subsequently found to be effective in dramatic case series (Perry and Jacobs, 1982) and were even efficacious in one small randomised controlled trial. (McCall et al., 1992) Barbiturates have largely been replaced by benzodiazepines, which have appeared effective in small uncontrolled studies, (Bush et al., 1996a) but the evidence does not meet high standards. (Zaman et al., 2019)

2.3 Diagnosis of catatonia

Contemporary definitions of catatonia have been codified in a manner that is agnostic to aetiology by DSM-5 and ICD-11. The criteria for diagnosis of catatonia in these two manuals are very similar, each requiring the presence of three of the clinical features. The features specified in DSM-5 are shown in Table 1.

Table 1: Features of catatonia in DSM-5 with definitions

Feature	Definition
Stupor	Alertness with minimal responsiveness to the environment
Catalepsy	After positioning by the examiner, postures are maintained
Waxy flexibility	Light and even resistance to the examiner moving the limbs
Mutism	Absent or minimal speech (not applicable if pre-existing aphasia)
Negativism	Refusal to obey commands or performance of an action contrary to instructions
Posturing	Spontaneous assumption and maintenance of a posture for an abnormally long period of time
Mannerism	Odd, exaggerated example of a normal action
Stereotypy	Repetitive, non-goal-directed movement
Psychomotor agitation	Hyperactivity unrelated to external stimuli
Grimacing	Spontaneous contortion of the facial muscles maintained for an abnormally long period of time
Echolalia	Repetition of another person's speech
Echopraxia	Copying another person's movements

(American Psychiatric Association, 2013; Denysenko et al., 2015; World Health Organization, 2018)

Other clinical features that are not part of these diagnostic criteria include ambitendency (indecisive, hesitant movements), verbigeration (repetitive speech, like a scratched record), *Gegenhalten* (resistance proportionate to the force exerted by the examiner), *Mitgehen* (limbs moving much further than a force applied by the examiner would justify) and automatic obedience (exaggerated compliance with commands). Autonomic instability (pyrexia, tachycardia, hypertension, increased respiratory rate and diaphoresis) in the presence of catatonia suggests the presence of malignant catatonia, a life-threatening variant of the syndrome.

Although catatonia has numerous possible symptom combinations, (Wilson et al., 2015) there are compelling reasons to study it as a single entity for the purposes of this thesis. Clinical and demographic factors can distinguish catatonia from other psychotic and affective disorders. (Peralta et al., 1997) In addition, different forms of catatonia (Kahlbaum's classical retarded catatonia, malignant catatonia and neuroleptic malignant syndrome) are highly comorbid. (Fink and Taylor, 2006) In terms of treatment, response rates to benzodiazepines and electroconvulsive therapy (ECT) are high, regardless of the aetiology of the catatonia. (Barnes et al., 1986) Moreover, catatonia is not a common disorder, so pragmatically to study it in depth, it is helpful to consider it as a whole.

In addition to diagnostic criteria, various rating scales have been produced for clinical and research use, including the Bush-Francis Catatonia Rating Scale (BFCRS), Rogers Catatonia Scale, Modified Rogers Scale, Northoff Catatonia Rating Scale, Bräunig Catatonia Rating Scale and Kanner Scale, (Sienaert et al., 2011) in addition to more specialised instruments for use in certain subpopulations, such as the Pediatric Catatonia Rating Scale (for children and adolescents) (Benarous et al., 2016) and the Attenuated Behaviour Questionnaire (for individuals with autism). (Breen and Hare, 2017) The most widely used instrument is the BFCRS, which consists of 23 items rated from 0 to 3, giving a total score out of 69. (Bush et al., 1996a)

The disorders underlying catatonia are many and varied. In terms of terminology, I note there is controversy over the use of the traditional functional-organic distinction, as it artificially dichotomises complex disorders. (Bell et al., 2020) For the purposes of this thesis, particularly in Chapter 6, I was interested in the pragmatic clinical distinction between cases of catatonia where there is considered to be an identifiable neuropathological process (which I term 'medical' catatonia) and those where catatonia is considered part of a primary mental disorder (which I term 'psychiatric' catatonia). While I acknowledge the imperfections of this terminology, there is benefit from a common language within this thesis.

The majority of cases of catatonia occur in the context of a major psychiatric disorder, such as depression, bipolar affective disorder, schizophrenia or schizoaffective disorder, but a substantial minority of approximately 20-25% are due to a general medical condition. (Smith et al., 2012) This figure is at least 50% in acute medical and surgical settings. (Oldham, 2018) About 70% of cases of catatonia due to a general medical condition (GMC) are due to a neurological disorder. (Carroll et al., 1994) A list of more common conditions associated with catatonia is given in Table 2.

Table 2: Common conditions underlying catatonia

Psychiatric conditions	**General condition**
• Depression • Schizophrenia • Mania • Autism • Tourette's syndrome • OCD	• CNS structural lesions (e.g. bilateral infarction of the parietal lobes, temporal infarcts, thalamic lesions, bilateral lesions in globus pallidus) • CNS infections (especially HSV, neurosyphilis) • HIV infection • Autoimmune encephalitis (especially NMDA receptor encephalitis) • Dementia (frontotemporal dementia, Alzheimer's disease, Lewy body dementia, Creutzfeldt Jakob disease)

	• Multiple sclerosis • Systemic lupus erythematosus • Thyroid disease • Vitamin B12 deficiency, nicotinic acid deficiency, pellagra • Wilson's disease • Drug toxicity (especially disulfiram, phencyclidine, steroids, and antipsychotics) • Drug withdrawal (especially benzodiazepines, clozapine) • Seizure

CNS, Central Nervous System; NMDA, N-methyl-D-aspartate; HIV, human immunodeficiency virus; HSV, human simplex virus

(Caroff et al., 2004; Carroll et al., 1994; Jaimes-Albornoz and Serra-Mestres, 2012)

2.4 Approaches to catatonia

Given the complexity of neuropsychiatric disorders such as catatonia, it is unlikely that any single approach will be able to adequately understand them. If we consider that catatonia as the pathological reversible disruption of structures supporting voluntary movement, there are several ways in which such disruptions might be elucidated. In this thesis, I consider four different approaches, two more indirect and two more direct. The more indirect approaches are the use of neuroimmunology, which may be able to identify upstream pathways that interfere with the neuronal processes underlying movement, and epidemiology, which may identify risk factors that suggest other causal mechanisms. The more direct approaches are structural neuroimaging, which may allow us to define to precise neuroanatomical structures that are disrupted in catatonia, and electroencephalography, which may be able to identify any alterations in spontaneous electrical activity with high temporal precision. In the following sections, I provide more detail as to the rationale for using each of these approaches.

2.5 Neuroimmunology

Immune dysregulation is gaining interest as a pathophysiological mechanism underlying neuropsychiatric disorders as diverse as narcolepsy, various dementias, depression, and psychosis, with converging evidence from biochemical, neuroimaging, and post-mortem studies. (Al-Diwani et al., 2017; Wohleb et al., 2016) In addition, genome-wide association studies have revealed that many of the single nucleotide polymorphisms associated with schizophrenia map onto the extended major histocompatibility complex, which codes for a range of proteins involved in adaptive immunity. (Ripke et al., 2011) 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. (Pollak, Rogers, et al., 2018)

The extent to which the immune system may play a role in the pathogenesis of catatonia has not previously been examined in an integrated way. Some evidence, such as that from related autoimmune movement disorders, has a rather indirect bearing. However, there are several studies that have examined inflammatory markers in catatonia or have linked catatonia to other autoimmune conditions, particularly NMDA receptor encephalitis. (Dalmau et al., 2008)

There are studies dating back several decades reporting catatonia in association with various infectious diseases. These rather disparate findings are in need of a synthesis to establish whether there is a coherent message about the aetiopathogenesis of catatonia. There is also a need to move beyond small samples to investigate the presence of inflammatory markers in catatonia.

2.6 Epidemiology

The majority of the existing literature on catatonia consists of case reports and case series (Weleff et al., 2022) with the effect that understanding the epidemiology of the condition from the published literature is difficult. Some work has been conducted on the prevalence of catatonia in various settings, as summarised in a meta-analysis of 74 studies, which found a mean prevalence of 9.4% (95% CI 6.9 to 11.7). (Solmi et al., 2018) However, the prevalence was much lower in larger studies where sample sizes were greater than 1000, giving a figure of 2.3% (95% CI 1.3 to 3.9). Such estimates are heavily dependent on the data collection method, as one study found prospective systematic ascertainment of catatonic features gave a prevalence of 18%, 7 times higher than the corresponding figures reliant on diagnoses given to the same patients in standard clinical care. (van der Heijden et al., 2005)

Moreover, it is unclear what the incidence of catatonia may be across the general population. Taylor and Fink (Taylor and Fink, 2003) estimated that 90,000 individuals in the USA experience catatonia annually based on psychiatric hospital admission data from 1996 to 1997, assuming that 10% of all psychiatric admissions and 20% of those with bipolar affective disorder experienced catatonia. Given a US population of 272,700,000 at this time, this gives an incidence of approximately 33.0 patient episodes per 100,000 person-years. However, this estimate heavily relies on figures on the proportion of psychiatric inpatients who experience catatonia, which as Solmi et al. (2018) demonstrated, are very heterogeneous.

There has been a suggestion in the literature that catatonia has been observed to 'virtually disappear', but this original assertion was not primarily based on empirical research. (Mahendra, 1981) Diagnoses of catatonia do appear to have dropped over the 20th century, (Morrison, 1974; Stompe et al., 2002; Tanskanen

et al., 2021) but it is contended that this may be at least in part due to underdiagnosis. (Fink and Taylor, 2009; Takács et al., 2021; van der Heijden et al., 2005) There is a need to calculate catatonia incidence at a population level more directly than previous estimates and to establish whether in recent years this has changed.

The longitudinal course of catatonia has also been poorly characterised and it is not clear to what extent catatonia represents a temporary state as opposed to an underlying predisposition that manifests with periodic relapses. (Walther and Strik, 2016) Gjessing described a periodic catatonia in the mid-20th century, but the most comprehensive study of catatonia relapse to date has been a case series of only 30 patients, finding that the number of episodes varied between 2 and 12. (Lin et al., 2016)

In terms of demographics, catatonia incidence appears to peak in middle age (Dutt et al., 2011) and have an approximately equal sex ratio. (Dutt et al., 2011; Parsanoglu et al., 2021) Previous smaller studies have suggested that prevalence of catatonia varies across different countries (World Health Organization, 1973) (although this was not confirmed by a recent meta-analysis) (Solmi et al., 2018) and between ethnic groups within the same country. (Chandrasena, 1986) Several studies have been suggestive of higher prevalence among patients of Black ethnicity, but these have been limited to specific patient groups, (Hutchinson et al., 1999; Lee et al., 2000) have lacked a control group (Dealberto, 2008) or have not been statistically significant; (Mustafa et al., 2012) all have been comparatively small.

Numerous studies have detailed medical complications in relation to catatonia, ranging from venous thromboembolism to pressure ulcers, muscle contractures and nutritional deficiencies. (Clinebell et al., 2014) If these reports are representative, this would have serious implications for the care of patients with catatonia, including in terms of urgency of diagnosis, treatment setting and the need for screening for complications. The ultimate test of the importance of such complications and whether catatonia is indeed a poor prognostic marker in psychiatric patients is whether mortality is any higher in catatonia. Catatonia was found to account for 32% of preventable deaths in one US study in state psychiatric hospitals. (Puentes et al., 2017) Older work found that patients with catatonic schizophrenia died at a younger age than patients with non-catatonic schizophrenia. (Niswander et al., 1963) More recent evidence came from a Japanese study that found that odds for mortality in a group of patients with schizophrenia and catatonic stupor was 4.8 times that in a comparison group of schizophrenia without catatonia. (Funayama et al., 2018) However, it is unclear how much results from catatonic stupor in schizophrenia can be generalised to the rest of the catatonia population. The mortality and morbidity of catatonia need to be ascertained and compared to similar patients without catatonia.

2.7 Neuroimaging findings

Perhaps the most familiar and utilised modality of investigation for neuropsychiatric disorders is neuroimaging. Neuroimaging may employ structural and functional methods across a range of imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and single-photon emission computerised tomography (SPECT).

A recent systematic review has examined neuroimaging findings in catatonia. (Haroche et al., 2020) Studies were generally small and the heterogeneity of methods makes it hard to compare findings. Among the 162 single cases reported in the literature, 77.8% had an underlying general medical condition, so they are unlikely to be representative of all catatonia cases. 76.4% had an abnormality in at least one modality of imaging, mostly diffuse brain changes, white matter abnormalities or multiple abnormalities.

In terms of larger studies using structural MRI, one study of 31 patients with catatonia (as defined in DSM-IV-TR) in whom an MRI had been performed for clinical reasons found diffuse atrophy in 18, focal atrophy in 4 (2 bifrontal and 2 cerebellar), focal encephalomalacia in 7 and multifocal changes in 3. (Smith et al., 2012) However, there was no comparison group, so it is not clear how this would compare to similarly selected patients without catatonia. In a subsequent study, 24 patients with schizophrenia spectrum disorder and catatonia (defined using the Northoff Catatonia Rating Scale [NCRS]) showed reduced grey matter volume in areas associated with the frontothalamic and corticostriatal networks compared to 22 patients who had schizophrenia spectrum disorder without catatonia. (Hirjak, Rashidi, et al., 2020) This study acknowledged that the included participants may not have had stable catatonic features, however. Another study of 30 patients with schizophrenia spectrum disorder and catatonia (defined using the NCRS) found reduced midbrain volumes compared to 29 patients with schizophrenia spectrum disorder without catatonia, but – paradoxically – among the catatonia group, there was a positive correlation between midbrain volume and NCRS score. (Fritze et al., 2020) Again, this study used patients with acute catatonia, so it was unclear how stable these changes may be. Finally, in a sign that this area is of increasing interest, a third study published in 2020 examined 86 patients with schizophrenia spectrum disorder, 43 of whom had a history of catatonia and 43 of whom did not, in comparison to 86 healthy controls. (Dean et al., 2020) Patients with schizophrenia spectrum disorder with and without catatonia showed smaller grey matter volumes compared to healthy controls, but there was no difference in brain structure between patients with and without catatonia. Unfortunately, there are several potential sources of bias in these case-control studies, often related to patient selection. For example, as prospective studies, they all specified that participants must be able to provide informed consent and they all excluded individuals with major medical and/or neurological comorbidities. (Dean et al., 2020; Fritze et al., 2020; Hirjak, Rashidi, et al., 2020) Both of these stipulations are likely to exclude some of the more unwell patients with catatonia. Given these biases and the inconsistency of previous results, it is clear that large, unbiased samples are required. There is also a need to

look at those with a history of catatonia to establish whether structural neuroimaging findings are trait or state.

Functional MRI in catatonia has shown various findings, including reduced activation of the supplementary motor area, reduced activation of the dorsolateral prefrontal cortex, hyperperfusion of the supplementary motor area and hyperperfusion of the ventromedial prefrontal cortex, (Scheuerecker et al., 2009; Walther et al., 2016) In terms of motor networks, patients with catatonia may have reduced intrinsic neural activity in regions within frontoparietal and frontotemporal motor networks as well as increased thalamocortical connectivity. (Walther et al., 2017) One study showed normalisation of fMRI changes in the orbitofrontal cortex during emotional processing following lorazepam treatment. (Richter et al., 2010) There has recently been a contention that neuroimaging studies using primarily motor or behavioural catatonia scales have highlighted regions involved in mediating dopaminergic neurotransmission, while those using the NCRS, which gives more weight to 'affective' signs of catatonia have found abnormalities in regions modulated by GABA and glutamate; (Hirjak, Kubera, et al., 2020) however, this theory has not been tested within individual studies investigating the impact of classifying patients under one system or another.

In summary, the case report literature suggests that structural neuroimaging findings are common, but this may be prone to reporting bias. One larger study found that abnormalities were common, but there was no comparison group without catatonia. The remaining literature has focussed on quantitative analysis of MRI scans, which may not correlate with the 'macroscopic' changes considered to be of relevance in a clinical MRI scan. There is a need for a structural neuroimaging study with a larger sample size and comparison to psychiatric patients without catatonia.

2.8 Electroencephalographic findings

Electroencephalography (EEG) was a technique first developed in the 1920s by the psychiatrist Hans Berger, with the aim of finding a physical basis for mental function. (La Vaque, 2008) However, apart from identifying occasional general medical 'mimics' of psychiatric disorders, the utility of the EEG in psychiatry has been limited, with abnormalities in primary psychiatric disorders tending to be nonspecific with poor correlation to current diagnostic categories. (Boutros et al., 2011) The primary use of the EEG in contemporary clinical practice is in the assessment of epilepsy, although it is also valuable in evaluating levels of consciousness, in localising lesions, and in the diagnosis of encephalitides and sleep disorders. (Teplan, 2002) Research using the EEG in psychiatric disorders has continued, however, motivated in part by its high temporal resolution and its ability to describe complex brain networks.

Attempts to characterise the EEG in catatonia date as far back as the 1950s in various populations. Findings have varied, including groups of spikes and abnormal responses to photic stimulation correlating with clinical state. (Gjessing et al., 1967; Hill, 1952, 1956) However, there has been little attempt to replicate these results.

More recently, Northoff and colleagues investigated the role of movement-related cortical potentials (*Bereitschaftspotentials*) on the EEG, finding that patients with catatonia showed significantly delayed potentials, relative to psychiatric and healthy controls. (Northoff et al., 2000)

From a clinical perspective, the utility of the EEG in catatonia is uncertain. While the diagnosis of catatonia itself is usually clear clinically, the presence of any underlying diagnosis – whether this is a general medical condition or a primary psychiatric diagnosis – may be less clear. (Oldham, 2018) Whether the EEG is of use in ascertaining (or at least in narrowing down) the underlying condition has yet to be established.

2.9 Aims and hypotheses

So far in this chapter, I have introduced the reader to the literature on the neuropsychiatry and epidemiology of catatonia. I have also highlighted some gaps that are particularly worthy of further study. Specifically these are as follows:

1. The neuroimmunology of catatonia relies on disparate findings that have yet to be synthesised into a coherent understanding. The only empirical studies have consisted of small sample sizes and there is a need to investigate inflammatory markers in larger groups of patients.
2. Regarding the epidemiology of catatonia, one of the most basic statistics – the population incidence of the disorder – is currently not known. Moreover, it is unclear whether and to what extent patients with catatonia differ from other patients with severe mental illnesses, in terms of demographic and clinical features.
3. In terms of structural neuroimaging, existing studies have been susceptible to selection and reporting biases and have produced inconsistent results. It is unclear what neuroimaging abnormalities occur in catatonia and whether they occur more or less frequently than in other psychiatric patients.
4. Concerning EEG findings in catatonia, there is a clinical need to establish whether the EEG assists in ascertaining the aetiology of catatonia, but the existing literature consists of numerous small studies that are individually unable to address this.

Having established these important lacunae in the scientific literature, the following sections of this chapter seek to address them by presenting the aims and objectives for the subsequent work. Some of these aims are descriptive, while others are hypothesis-driven.

2.9.1 Aim 1: To characterise the neuroimmunology of catatonia

Objective		**Chapter**
1.1	To examine the existing evidence for the involvement of the immune system in catatonia.	3

1.2	To compare clinical blood-based markers of inflammation and cell damage (C-reactive protein, iron, white cell count, creatine kinase and NMDA receptor antibodies) in psychiatric inpatients with and without catatonia in a case-control study using routinely collected electronic healthcare records. • Hypothesis: Blood-based markers of inflammation and cell damage will provide more evidence of peripheral inflammation in catatonia.	4

2.9.2 Aim 2: to characterise the epidemiology of catatonia

Objective		**Chapter**
2.1	To estimate the incidence of catatonia in an urban UK population.	4
2.2	To compare the age, sex and ethnic groups of psychiatric inpatients with and without catatonia in a case-control study.	4
2.3	To compare the mortality and admission duration of psychiatric inpatients with and without catatonia in a cohort study. • Hypothesis: Patients with catatonia will have a higher mortality and admission duration.	4

2.9.3 Aim 3: To characterise the structural neuroimaging findings in catatonia

Objective		**Chapter**
3.1	To classify and describe the abnormalities reported in clinical neuroradiological reports of patients with catatonia in a case-control study.	5
3.2	To compare the frequency of abnormalities reported in clinical neuroradiological reports of psychiatric patients with catatonia to those reported in other psychiatric patients referred for an MRI scan in a case-control study. • Hypothesis: MRI abnormalities will be more commonly reported in patients with catatonia.	5

2.9.4 Aim 4: To characterise the EEG findings in catatonia

Objective		Chapter
4.1	To classify and describe the abnormalities reported in clinical EEG reports of patients with catatonia in a systematic review.	6
4.2	To ascertain the performance of the EEG in determining whether catatonia has an underlying general medical condition or a primary psychiatric disorder in a meta-analysis. • Hypothesis: EEG abnormalities will be more commonly reported in patients with catatonia due to a general medical condition	6

3 The immunology of catatonia

This chapter has previously been published in an adapted form in The Lancet Psychiatry. (Rogers et al., 2019) *Various changes have been made since the original published article. Notably, the three systematic searches have been rerun and updated, which has significantly increased the number of included case reports and other studies. In addition, some of the interim conclusions were modified slightly, for example, introducing more caveats as to the evidence based on catatonia treatments. Further, I added some additional foundational text explaining the normal physiological function of the immune system. Changes have also been made to integrate this chapter with the rest of the thesis manuscript.*

3.1 Summary

This chapter addresses Aim 1 of the thesis by examining the evidence for the role of the immune system in catatonia in the form of a narrative review, informed by systematic literature searches. 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 are associated with it. The most common form of autoimmune catatonia is *N*-methyl-*D*-aspartate receptor (NMDAR) encephalitis, which can account for the full spectrum of catatonic features. Autoimmunity appears to induce 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.

3.2 Background

As discussed in section 2.5, interest in the role of immune system in a wide range of neuropsychiatric conditions is growing. However, to date, there has been little systematic work on its potential role in catatonia, despite intriguing findings relating to the innate and adaptive immune system, deriving from historical reports of infections linked to catatonia, related autoimmune conditions and direct evidence of inflammatory markers in catatonia.

In this chapter, I discuss the evidence for the involvement of the immune system in catatonia, addressing Objective 1.1 of Aim 1 of this thesis. This appears to be a valuable line of enquiry, given the wide range of infective and inflammatory conditions that can underlie catatonia. I address whether the immune system plays a role in catatonia, using some direct and some more circumstantial evidence, and endeavour to establish specific models for this. I 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. I have

structured the chapter by first considering how catatonia can be associated with various infectious diseases, before considering the putative role of the innate immune system and then the role that autoimmunity may play.

This chapter constitutes a narrative review, which was informed by several systematic searches. This has allowed me to provide an overview of a broad question whilst simultaneously being able to provide comprehensive coverage of several more specific questions. The initial search used PubMed with the term "catatoni*" in association with any of the following terms: "immune*", "infection*", "inflame*", "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 disorders underlying catatonia, autoimmune disorders underlying catatonia and inflammatory markers in catatonia. To conduct these, I searched 6 databases (AMED, BNI, CINAHL, EMBASE, Medline, PsycINFO and PubMed) for catatonia in conjunction with relevant specific search terms (e.g. "infect*", "virus", "bacteria" etc). After de-duplication, I screened articles on titles and abstracts before reviewing relevant full text articles to systematically construct tables in this chapter. Only articles with full texts or sufficiently detailed abstracts in English were included. The original search software (NICE Healthcare Databases Advanced Search) is now defunct, so the three systematic searches were revised with an updated search to January 23 2023 using Ovid, which was used to search Ovid MEDLINE® ALL, Embase Classic+Embase, APA PsycINFO and AMED (Allied and Complementary Medicine). This updated search is shown in Table 3.

Table 3: Search terms for systematic literature searches on catatonia in relation to infectious diseases, autoimmune diseases and immunological biomarkers

Search	**Search terms**
Catatonia in infectious diseases	1. (infect* or virus or viral or bacteria* or fung* or 46iffer46o* or prion).mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 2. exp Bacterial Infections/ 3. exp Mycoses/ 4. exp Parasitic Diseases/ 5. exp Virus Diseases/ 6. exp Catatonia/ 7. exp Schizophrenia, Catatonic/ 8. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm]

	9. 1 or 2 or 3 or 4 or 5 10. 6 or 7 or 8 11. 9 and 10 12. limit 11 to dt=20180930-20230123 13. 12 use medall 14. (infect* or virus or viral or bacteria* or fung* or 47iffer47o* or prion).mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 15. exp infection/ 16. exp catatonia/ 17. exp catatonic schizophrenia/ 18. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 19. 14 or 15 20. 16 or 17 or 18 21. 19 or 20 22. limit 21 to dd=20180930-20230123 23. 22 use emczd 24. (infect* or virus or viral or bacteria* or fung* or 47iffer47o* or prion).mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 25. exp Infectious Disorders/ 26. cataton*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 27. exp Catatonia/ 28. exp Catatonic Schizophrenia/ 29. 24 or 25 30. 26 or 27 or 28 31. 29 and 30 32. limit 31 to up=20180930-20230123 33. 32 use psyh 34. exp Infection/ 35. (infect* or virus or viral or bacteria* or fung* or 47iffer47o* or prion).mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 36. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 37. exp Catatonia/ 38. 34 or 35 39. 36 or 37 40. 38 and 39

	41. limit 40 to up=20180930-20230123 42. 41 use amed 43. 13 or 23 or 33 or 42
Catatonia in autoimmune diseases	1. autoimmune.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 2. exp Autoimmune Diseases/ 3. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 4. exp Catatonia/ 5. 1 or 2 6. 3 or 4 7. 5 and 6 8. limit 7 to dt=20180930-20230123 9. 8 use medall 10. autoimmune.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 11. exp autoimmune disease/ 12. cataton*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 13. exp catatonia/ 14. 10 or 11 15. 12 or 13 16. 14 and 15 17. limit 16 to dd=20180930-20230123 18. 17 use emczd 19. autoimmune.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 20. exp Immunologic Disorders/ 21. cataton*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 22. exp Catatonia/ 23. 19 or 20 24. 21 or 22 25. 23 and 24 26. limit 25 to up=20180930-20230123 27. 26 use psyh 28. autoimmune.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm]

	29. exp Autoimmune disease/ 30. exp Catatonia/ 31. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, tc, id, tm] 32. 28 or 29 33. 30 or 31 34. 32 and 33 35. limit 34 to up=20180930-20230123 36. 35 use amed 37. 9 or 18 or 27 or 36 38. remove duplicates from 37
Immunological and related biomarkers in catatonia	1. (biomarker or "white cell" or leukocyte or neutrophil or basophil or lymphocyte or platelet or calcium or magnesium or potassium or sodium or "liver function" or ALT or "alanine transaminase" or AST or "aspartate transaminase" or GGT or "gamma glutamyl transferase" or ALP or "alkaline phosphatase" or iron or ferritin or transferrin or "creatine kinase" or "creatine phosphokinase" or CK or CPK or LDH or "lactate dehydrogenase" or "D-dimer" or "C-reactive protein" or CRP or "erythrocyte sedimentation rate" or ESR or "plasma viscosity" or fibrinogen or interleukin or "tumour necrosis factor" or TNF or interferon or IFN or "alpha-1-antitrypsin" or myeloperoxidase or MPO).mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx, tc, id, tm] 2. exp Catatonia/ 3. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx, tc, id, tm] 4. 2 or 3 5. 1 and 4 6. limit 5 to dt=20180930-20230123 7. 6 use medall 8. (biomarker or "white cell" or leukocyte or neutrophil or basophil or lymphocyte or platelet or calcium or magnesium or potassium or sodium or "liver function" or ALT or "alanine transaminase" or AST or "aspartate transaminase" or GGT or "gamma glutamyl transferase" or ALP or "alkaline phosphatase" or iron or ferritin or transferrin or "creatine kinase" or "creatine phosphokinase" or CK or CPK or LDH or "lactate dehydrogenase" or "D-dimer" or "C-reactive protein" or CRP or "erythrocyte sedimentation rate" or ESR or "plasma viscosity" or fibrinogen or interleukin or "tumour necrosis factor" or TNF or interferon or IFN or "alpha-1-antitrypsin" or myeloperoxidase or MPO).mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx, tc, id, tm] 9. exp catatonia/

	10. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx, tc, id, tm] 11. 9 or 10 12. 8 and 11 13. limit 12 to dd=20180930-20230123 14. 13 use emczd 15. (biomarker or "white cell" or leukocyte or neutrophil or basophil or lymphocyte or platelet or calcium or magnesium or potassium or sodium or "liver function" or ALT or "alanine transaminase" or AST or "aspartate transaminase" or GGT or "gamma glutamyl transferase" or ALP or "alkaline phosphatase" or iron or ferritin or transferrin or "creatine kinase" or "creatine phosphokinase" or CK or CPK or LDH or "lactate dehydrogenase" or "D-dimer" or "C-reactive protein" or CRP or "erythrocyte sedimentation rate" or ESR or "plasma viscosity" or fibrinogen or interleukin or "tumour necrosis factor" or TNF or interferon or IFN or "alpha-1-antitrypsin" or myeloperoxidase or MPO).mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx, tc, id, tm] 16. exp Catatonia/ 17. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx, tc, id, tm] 18. 16 or 17 19. 15 and 18 20. limit 19 to up=20180930-20230123 21. 20 use psyh 22. (biomarker or "white cell" or leukocyte or neutrophil or basophil or lymphocyte or platelet or calcium or magnesium or potassium or sodium or "liver function" or ALT or "alanine transaminase" or AST or "aspartate transaminase" or GGT or "gamma glutamyl transferase" or ALP or "alkaline phosphatase" or iron or ferritin or transferrin or "creatine kinase" or "creatine phosphokinase" or CK or CPK or LDH or "lactate dehydrogenase" or "D-dimer" or "C-reactive protein" or CRP or "erythrocyte sedimentation rate" or ESR or "plasma viscosity" or fibrinogen or interleukin or "tumour necrosis factor" or TNF or interferon or IFN or "alpha-1-antitrypsin" or myeloperoxidase or MPO).mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx, tc, id, tm] 23. exp Catatonia/ 24. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx, tc, id, tm] 25. 23 or 24 26. 22 and 25 27. limit 26 to up=20180930-20230123 28. 27 use amed

	29. 7 or 14 or 21 or 28 30. remove duplicates from 29

3.3 Catatonia due to infection

A systematic review reported that 20% of cases of catatonia have an underlying general medical disorder, of which CNS inflammation (comprising both infective and immune disorders) accounts for 29%. (Oldham, 2018) Numerous infectious diseases have been reported to trigger catatonia. From a search of the existing literature (Table 4), I identified 195 patients who have had catatonia in association with an infectious disease, of whom the majority of cases were published as case reports, with the remaining ones as case series. Laboratory evidence of infection (such as isolation of the organism in the serum, or viral DNA in the cerebrospinal fluid) was reported in 91 of the cases (46.7%). A robust temporal association between the infection and catatonia was reported in 94 of the cases (48.2%). A prior psychiatric disorder was recorded in 32 cases (16.4%) and a prior medical disorder in 51 cases (26.2%), although an absence of a pre-existing condition was often not stated. Only 107 of the cases (54.9%) recorded the presence of at least two features from the Bush-Francis Catatonia Screening Instrument. (Bush et al., 1996a) In some cases, the catatonia resolved with antimicrobial therapy, (Pfister et al., 1993) whilst in others, it required treatment with benzodiazepines (Snyder et al., 1992) or electroconvulsive therapy. (Säll et al., 2009)

Table 4: Case reports and series of Infectious diseases reported in association with catatonia

Infectious disease	**Number of cases**	**Suspected organisms**
Bacterial meningitis / encephalitis	5	*Borrelia burgdorferi* (4), unspecified (1)
Viral meningitis / encephalitis	29	*Adenovirus* (1), *Cytomegalovirus* (1), *Epstein Barr virus* (1), *HHV6* (1), *Herpes simplex virus* (10), *Japanese encephalitis virus* (1), *Measles virus* (3), *Tick-borne encephalitis virus* (1), *Varicella zoster virus* (1), *West Nile virus* (1), unspecified (9)
Cerebral malaria	4	*Plasmodium falciparum* (2), unspecified (2)
CNS infection unspecified	3	Unspecified (3)
Respiratory tract infection	64	*Aspergillus* (1), *Influenza* (1), *Mycoplasma* (1), *Klebsiella* (1), *Epstein Barr Virus* (1), SARS-CoV-2 (50), *Streptococcus* (4), unspecified (5)
HIV-related	22	HIV (20), HIV and *John Cunningham (JC) virus* (2)

Syphilis	4	*Treponema pallidum* (4)
Systemic bacterial infection	36	*Coxiella burnetti* (1), *Rickettsia* (1), *Salmonella typhi* (30), *Staphylococcus aureus* (1), *Streptococcus* (2), unspecified (1)
Systemic viral infection	4	*Cytomegalovirus* (2), *Epstein Barr virus* (1), *Flavivirus* (1)
Prion-related disorders	8	*PrP* (8)
Other	16	*Tropheryma whipplei* (1), *E. coli* (1), *Mycobacterium tuberculosis* (1), *Taenia solium* (2), *Chlamydia trachomatis* (1), *Trypanosoma cruzi* (1), unspecified (9)
Total	195	-

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. Among the viral triggers, neurotropic viruses were often – though not exclusively – implicated.

The immunological response may also be important, given that in some neurological disorders, such as meningoencephalitis, damage is caused primarily by the immune reaction. (Waisman et al., 2015) 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) (see section 3.5.3), (Elia et al., 2005) or in *N*-methyl-*D*-aspartate receptor (NMDAR) encephalitis purportedly triggered by yellow fever vaccination, (Hozáková et al., 2018) HSV infection (Schein et al., 2017) or EBV infection. (Derksen et al., 2013) In cases of pyrexia of unknown origin, an infective cause was often assumed, but it is possible that another disorder was responsible. (Powers et al., 1976; Unni et al., 1995)

The relationship to SARS-CoV-2 merits special attention, given the 50 reported cases. There is a plausible pathophysiological relationship given that several cases of NMDA receptor encephalitis, which has a robust relationship with catatonia (discussed below), have been reported after a supposed trigger by SARS-CoV-2 infection. (Vasilevska et al., 2021) A small study also suggested that catatonia presentations in a child psychiatry unit increased during the COVID-19 pandemic. (Ghumman et al., 2022). However, some caution is due for several reasons: I have previously examined the literature on neuropsychiatric manifestations of prior epidemic coronaviruses and catatonia has not featured. (Rogers et al., 2020) Moreover, given the near-ubiquity of SARS-CoV-2 infection after a couple of years since the emergence of the pandemic, it is reasonable to suppose that many cases of coincident catatonia and COVID-19 would occur merely by chance. Some

evidence for this may come from the fact that 21 of the 50 COVID-19 cases (42%) reported a prior psychiatric disorder, compared to only 18 of the 145 non-COVID-19 cases (12.4%), suggesting that other reasons for catatonia may have been more prominent in the COVID-19 group. In addition, there is precedent for spurious associations with COVID-19 driven by case reports to be undermined by subsequent larger observational studies, as has occurred with Guillain-Barré syndrome. (Keddie et al., 2020) It appears this may have happened with catatonia as well, as a recent study using the US National Inpatient Sample Analysis with data from 2020 suggests. (Luccarelli et al., 2022) This found that of an estimated 15,965 catatonia diagnoses, only 610 (3.7%) occurred in the same admission as a COVID-19 infection. Overall, a diagnosis of catatonia was *negatively* associated with a diagnosis of COVID-19. While there may be individual occasions where catatonia is triggered by COVID-19, this did not seem to be a major factor in catatonia incidence, even during the height of the COVID-19 pandemic.

3.4 Innate immune system

The innate immune system provides a rapid cellular and humoral immune response, reliant on germline-encoded receptors. (Turvey and Broide, 2010) Barrier functions of the body, including that of the skin and mucosal epithelia are sometimes also considered to be part of the innate immune system. (Elias, 2007)

3.4.1 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 interaction, (Wohleb et al., 2016) all of which are commonly apparent in catatonia. Psychomotor activity may also be slowed in mild experimentally induced infection. (Smith et al., 1987) This may be due to aberrant activity in parts of the brain involved in interoception and impaired spatial memory performance. (Harrison et al., 2009, 2014) Hence it is possible that the brain's response to inflammation, if severe, could result in a complex movement disorder such as catatonia.

In response to an acute stressor, immune cell trafficking occurs with the movement of leukocytes to, and within, a target organ. (Workman and Nelson, 2011) However, in chronic stress, increased monocyte production and microglial activation result in neuroinflammation and are associated with depressive behaviour. (Wohleb et al., 2016) Depression is often associated with raised levels of pro-inflammatory cytokines, granulocytes, and monocytes. (Wohleb et al., 2016) Regarding subtypes of depression, it is atypical depression, which is characterised by mood reactivity, hyperphagia, hypersomnia, and the catatonia-like phenomenon of leaden paralysis, (Singh and Williams, 2006) which is most associated with raised inflammatory markers. (Penninx et al., 2013) Conversely, psychomotor retardation is more commonly seen in melancholic depression, which is less associated with a peripheral pro-inflammatory state. (Penninx et al.,

2013) 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. (Workman and Nelson, 2011)

3.4.2 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%). (Funayama et al., 2018; Rasmussen et al., 2016) Given that there are no clinical features that can reliably distinguish NMS from malignant catatonia, (Carroll and Taylor, 1981) some authors consider NMS to be a specific form of antipsychotic-induced malignant catatonia. (Fink, 1995) It is common for residual catatonia to remain after the resolution of the full syndrome of NMS. (Caroff et al., 2000)

There is some suggestion that inflammation may be important to the pathophysiology of NMS, with acute phase responses such as leukocytosis, thrombocytosis, and ferropoenia frequently reported. (Anglin et al., 2010; Rosebush and Stewart, 1989) Low serum iron (discussed in more detail in section 3.4.3) has particularly emerged as a sensitive biomarker. (Anglin et al., 2010; Rosebush and Stewart, 1989) It has been hypothesised that in NMS pro-inflammatory cytokines may reduce the levels of the neuroprotective kynurenic acid, impairing the activity of dopaminergic neurons in the midbrain, causing exquisite sensitivity to a further antipsychotic-induced reduction in dopaminergic signalling. (Oruch et al., 2017) It is possible, however, that an inflammatory profile in the blood may be the consequence of rhabdomyolysis, rather than the primary pathology.

3.4.3 Direct evidence for the acute phase response in catatonia

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. (Gruys et al., 2005; Markanday, 2015) 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 5. 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 might be argued to be the result of muscular rigidity and excessive immobilisation rather than indicating a primary muscular pathology. In one study, a raised CK predicted a good response to treatment with lorazepam. (Northoff et al., 1996)

Table 5: Studies of inflammatory markers in catatonia

Laboratory marker	**Study**	**Subjects with catatonia**	**Controls**	**Results**
White cell count	Haouzir et al. (2009)	25 patients with acute catatonia	50 patients without catatonia with similar underlying diagnoses	No difference in white cell count
	Rao et al. (2011)	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)	12 patients with schizophrenia and catatonia	87 patients with schizophrenia without catatonia	hsCRP significantly higher in patients with catatonia
	Zhou et al. (2020)	51 patients with catatonia	55 healthy controls	hsCRP significantly higher in patients with catatonia
Iron	Haouzir et al. (2009)	25 patients with acute catatonia	50 patients without catatonia with similar	Non-significant for lower iron in catatonia group

			underlying diagnoses	
	Lee (1998)	39 patients with catatonia in psychiatric intensive care units	None	17 patients had iron below reference range
	Peralta (1999)	40 with psychosis and catatonia	40 with psychosis without catatonia	Iron significantly lower in patients with catatonia
	Carroll & Goforth (1995)	12 episodes of catatonia in 11 psychiatric inpatients	None	3 patients demonstrated iron below reference range
	Lakshmana et al. (2009)	40 patients with catatonia	Age- and sex-matched psychiatric patients (*n* not stated)	No difference in iron compared between groups
	Zingela et al. (2022)	44 patients with catatonia	None	20 patients had low iron levels
Creatine kinase (CK)	Northoff et al. (1996)	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)	25 patients with acute catatonia	50 patients without catatonia patients with similar diagnoses to those with catatonia	No difference in CK levels
	Meltzer (1968)	2 patients with catatonia	14 patients with non-catatonic psychoses	No difference in CK levels
	Zingela et al. (2022)	44 patients with catatonia	None	24 patients had high CK levels
D-dimer	Haouzir et al. (2009)	25 patients with acute catatonia	50 patients without catatonia with similar diagnoses to patients with catatonia	D-dimer significantly higher in patients with catatonia

One study found the acute phase marker, and fibrin degradation product, D-dimer to be raised in all 25 patients with catatonia tested, with a mean value three times higher than in psychiatric patients without catatonia. (Haouzir et al., 2009) 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 two studies and found to be raised in patients with catatonia relative to individuals with schizophrenia or healthy controls, but the absolute concentration of CRP was not very high in either study. (Akanji et al., 2009; Zhou et al., 2020)

Low serum iron was originally hypothesised to be present in catatonia given the similarities to NMS. Low serum iron is an established feature of the acute phase response and arises due to the upregulated production of ferritin and hepcidin by the liver, possibly as a way of depriving invading pathogens of iron. (Northrop-Clewes, 2008) Three uncontrolled studies have shown that between 25% and 44% of catatonic episodes were accompanied by serum iron levels below the reference range. (Carroll and Goforth, 1995; Lee, 1998; Zingela et al., 2022) When patients with catatonia have been compared to psychiatric controls, however, the results have been equivocal. (Haouzir et al., 2009; Lakshmana et al., 2009; Peralta et al., 1999)

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. In several studies, low serum iron in catatonia has been associated with the subsequent development of NMS. (Carroll and Goforth, 1995; Lee, 1998; Raja et al., 1994) This may be because iron is a cofactor for tyrosine hydroxylase, the rate-limiting step in dopamine synthesis, (Daubner et al., 2011; Kim and Wessling-Resnick, 2014) so a combination of low iron impairing dopamine production and antipsychotic medications blocking dopamine receptors results in the pathological hypodopaminergic signalling characteristic of NMS.

3.4.4 Implications of catatonia treatment for inflammatory hypotheses

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. (Prud'homme et al., 2015) Lymphocytes express GABA-A receptors and activation of these receptors reduces the production of pro-inflammatory cytokines. (Prud'homme et al., 2015) However, one study specifically in catatonia found higher monocyte counts predicted benzodiazepine non-response. (Rao et al., 2011) 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. (Fernández Hurst et al., 2017; Ramirez et al., 2016) 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. (Fernández Hurst et al., 2017) 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. (Hsu et al., 2017; Huang et al., 2014) However, given that the effect of benzodiazepines in catatonia can occur rapidly within minutes, it is perhaps unlikely that a rather indirect immune-mediated mechanism is a major part of their activity.

Regarding ECT, a single session appears to activate the immune system, increasing levels of the cytokines IL-1β, IL-6, IL-10, and TNF-α. However, a course of several sessions of electroconvulsive stimulation appears to down-regulate immune system activity, at least in animal studies. (Guloksuz et al., 2014)

Minocycline is an antimicrobial that also has anti-inflammatory properties. (Keller et al., 2013) It has been shown to prevent stress-induced microglial changes in rodents (Wohleb et al., 2016) and has been proposed as an adjunctive treatment for schizophrenia. (Solmi et al., 2017) There is some evidence to suggest that it

may reduce negative symptoms in schizophrenia, (Levkovitz et al., 2009) some of which (such as poverty of speech, affective blunting, and avolition) overlap with catatonia. However, a more recent double-blinded, randomised study, which specifically aimed to examine the effect of minocycline on negative symptoms, did not find any benefit. (Deakin et al., 2018) No studies of which I am 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. (Ahuja and Carroll, 2007; Miyaoka et al., 2007)

3.4.5 The evidence for innate immunity in catatonia

I 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. (Nievas et al., 2011)

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. (Northoff, 2002) 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 4 demonstrates, the infective disorders underlying 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.

3.5 Autoimmunity

Autoimmunity entails an imbalance of effector and regulatory elements of the immune system, involving impaired control of self-reactive lymphocytes. (Rosenblum et al., 2015)

3.5.1 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. I 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). (Hadavi et al., 2011) GAD is an enzyme that converts glutamate to GABA, though the pathogenicity of GAD autoantibodies, which are intracellular, in SPS is not established. SPS bears several similarities to catatonia and one author has suggested testing for GAD autoantibodies to distinguish between them. (Rasmussen et al., 2016) They share immobility, an emotionless facial expression and marked anxiety. Moreover, hypertonic episodes in SPS can have psychological triggers. (Hadavi et al., 2011) 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 (PERM), responds dramatically to immunosuppression. (Chang et al., 2013) PERM has been linked with the presence of antibodies to the glycine receptor and DPPX. (Balint et al., 2014; Crisp et al., 2017; Hutchinson et al., 2008)

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. (Scammell, 2015) More 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. (Tsutsui et al., 2012) 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. (Antelmi et al., 2017) 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 6.

Table 6: Comparison of catatonia and cataplexy (in the context of narcolepsy)

	Catatonia	**Cataplexy**
Trigger	Strong negative emotions	Strong positive emotions
Tone	Often increased with rigidity; 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 and positive allosteric modulators	Antidepressants, sodium oxybate (GABA-B agonist)
Duration	Days-weeks	Up to 2 minutes (longer in status cataplecticus)

3.5.2 Autoimmune disorders associated with catatonia

Autoimmune disorders underlying catatonia are shown in Table 7 as the results of a literature search. The majority are represented by case reports and case series, although there are some larger case series and cohort studies for NMDAR encephalitis, as shown in Table 8. 366 of the cases (62.4%) recorded at least two features from the Bush-Francis Catatonia Screening Instrument. (Bush et al., 1996a) 38 patients (6.5%) recorded a prior psychiatric disorder and 48 (8.2%) 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 precipitant of the catatonia. In a few, the autoimmune disorder was a more distal event, 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. (Koenig et al., 2005)

Table 7: Case reports and series of cases of autoimmune disorders reported in association with catatonia

Category of autoimmunity	***n***	**Specific disorder**	***n***
Autoimmune thyroid disorders	19	Hyperthyroid state	4
		Hypothyroid state	6
		Euthyroid state with thyroid antibodies	6
		Thyroid state not stated	3
Autoimmune encephalitis	479	Acetylcholine receptor ganglionic neuronal antibody encephalitis	1
		GABA-AR encephalitis	2
		GAD encephalitis	4
		LGI-1 encephalitis	1
		Neurofilament heavy chain encephalitis	1
		NMDAR encephalitis	436
		Progressive encephalomyelitis with rigidity and myoclonus (PERM)	2
		Voltage-gated calcium channel (VGCC) encephalitis	1
		'Voltage-gated potassium channel (VGKC) complex' encephalitis*	4

		Unspecified or seronegative	27
Demyelinating disorders	14	Acute disseminated encephalomyelitis	3
		Multiple sclerosis	10
		Neuromyelitis optica	1
Pernicious anaemia	3	Pernicious anaemia	3
Systemic lupus erythematosus (SLE) and related	64	Antiphospholipid syndrome	2
		SLE	62
Other	8	Addison's disease	1
		Crohn's disease	1
		MOG antibody disease	1
		Paediatric autoimmune neuropsychiatric syndrome (PANS)	2
		Neurosarcoidosis	1
		Sjögren's syndrome	2
Total	587		

*More recent evidence has found that the pathogenic antibodies are actually directed against the LGI1 and CASPR2 sites. (Michael et al., 2020)

In addition, it is notable that the 22q11.2 deletion syndrome, which features thymic aplasia and a resultant absence of peripheral T-cells, (Kobrynski and Sullivan, 2007) has also been linked to catatonia. (Butcher et al., 2018) 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 7 is that 74.3% of all cases of autoimmune catatonia reported are due to NMDAR encephalitis, despite the fact that the disorder was only described in 2007. (Dalmau et al., 2007) Before discussing this finding of autoimmunity directed against the CNS in depth, I 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. (Nagao and Hirokawa, 2017) In addition to the well-known features of impaired proprioception, depression, and dementia, three cases of catatonia in pernicious anaemia have been reported, all of which responded to vitamin B12 supplementation. (Abi-Abib et al., 2010; Bram et al., 2015; Jauhar et al., 2010) However, dietary vitamin B12 deficiency may also underlie catatonia, (Berry et al., 2003; Catalano et al.,

1998) which suggests it may be the vitamin deficiency rather than the autoimmunity *per se* that causes the catatonia.

In thyroid disease, catatonia has been reported in patients with thyroid autoantibodies with hyperthyroid, (Bharadwaj et al., 2012; Saito et al., 2012; Urias-Uribe et al., 2017) hypothyroid (Lee and House, 2017; Shlykov et al., 2016) and euthyroid states. (Chen et al., 2015; Lalanne et al., 2016) However, catatonia has also occurred in hypothyroidism due to thyroidectomy, (Iskandar et al., 2014) so it is unclear whether thyroid status or the presence of the autoantibodies is the causally relevant factor.

In systemic lupus erythematosus (SLE), 62 cases of catatonia have been reported, generally with high titres of antinuclear antibody (ANA), a non-specific antibody, and anti-double-stranded DNA (anti-dsDNA), which is much more specific to SLE. (Pisetsky and Lipsky, 2020). 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. (Ferrafiat et al., 2017)

3.5.3 Autoimmune disorders directed at CNS targets causing catatonia

Autoimmune encephalitides, as examples of autoimmune disorders directed at CNS targets, merit special consideration. T-cell-mediated disorders, such as acute demyelinating encephalomyelitis (ADEM) can occasionally present with catatonia. (Bachmann and Schröder, 2006) However, catatonia is more commonly a feature of autoimmune encephalitides associated with antineuronal antibodies. There are several mechanisms by which these antibodies can impair the function of their targets on the neuronal cells surface. These include internalisation of the antigens; activation of complement, resulting in formation of the membrane attack complex and cell damage; direct blockade of receptor function; and impairing the interaction between the target protein and other proteins. (Giannoccaro et al., 2020)

Given the centrality of benzodiazepines in treatment for catatonia, it is unsurprising that catatonia has been reported in two patients with GABA-AR antibodies. (Nikolaus et al., 2018; Pettingill et al., 2015) It is possible that catatonia may be more common, as there has not hitherto been careful psychiatric phenotyping among this population. (Petit-Pedrol et al., 2014) 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, which suggests that such autoantibodies might not be present at stable levels in the serum. (Pettingill et al., 2015)

NMDAR encephalitis – where antibodies to the post-synaptic NMDA glutamate receptor cause cross-linkage and internalisation of the receptor – is increasingly considered as a neurological 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. (Al-Diwani et al., 2017; Dalmau and Graus, 2018) In fact, the association with catatonia seems to be even stronger than the association with psychosis. (Dalmau et al., 2008) Where catatonia is reported, it is often malignant catatonia and tends to co-occur with psychosis (McCarthy et al., 2012) and mania. (Consoli et al., 2011) Table 8 summarises the case series and cohort studies where $n \geq 10$ in which the authors have specified whether catatonia was present. A minimum of a sample size of 10 was chosen as a compromise between reducing selection bias and including a range of studies in different settings. The range of catatonic features reported is wide and includes echolalia, grimacing, posturing and alternating hypermotor and hypomotor activity. (Dalmau et al., 2008) There is also evidence that the presence of catatonia in NMDAR encephalitis is a poor prognostic marker, being associated with a higher score on the Modified Rankin Scale and increased risk of deep vein thrombosis, pressure sores, pneumonia and intensive care unit admission. (Wu et al., 2023)

Table 8: Prevalence of catatonia (as identified by authors) in case series of NMDAR encephalitis

Study	Participants	Cases of catatonia	%
Dalmau et al., 2008 (Dalmau et al., 2008)	100	88	88.0
Kruse et al., 2015 (Kruse et al., 2015)	12	9	75.0
Duan et al., 2016 (Duan et al., 2016)	28	19	67.9
Granata et al., 2018 (Granata et al., 2018) [a]	18	8	44.4
Herken and Prüss, 2017 (Herken and Pruss, 2017) [b]	53	10	18.9
Herrera-Mora et al., 2021 (Herrera-Mora et al., 2021)	66	21	31.8
Espinola-Nadurille et al., 2022 (Espinola-Nadurille et al., 2022)	100	69	69.0
Warren et al., 2021 (Warren et al., 2021)	30	14	46.7
Adams et al., 2021 (Adams et al., 2021)	13	7	53.8
Hinotsu et al., 2022 (Hinotsu et al., 2022)	10	10	100
TOTAL	430	255	59.3

[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. In one study of 459 psychiatric patients, two had IgG antibodies against NR1a in serum and CSF; both had catatonia and were ultimately reclassified as NMDAR encephalitis. (Steiner et al., 2013) 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. (Kruse et al., 2015) 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. (Lin et al., 2017) 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. (Lennox et al., 2017) One study with individuals at ultra-high risk of psychosis suggests more severe catatonic features in individuals with NMDAR antibodies. (Pollak, Iyegbe, et al., 2018)

NMDAR encephalitis has only been described in the last decade but has led to a re-evaluation of encephalitis lethargica, (Dalmau et al., 2011) first recognised in 1917, due to certain similarities. (von Economo, 1917) Encephalitis lethargica is characterised by profound sleep impairment (insomnia, hypersomnia or sleep inversion), oculomotor abnormalities, a hypokinetic movement disorder and neuropsychiatric symptoms. (Reid et al., 2001) Although historically linked to the 1918 influenza pandemic, the evidence for a causal association is sparse. (Reid et al., 2001) More recently, investigations have found a high prevalence of antibodies to the NMDAR and the dopamine D2 receptor in the serum of children with encephalitis lethargica, raising the intriguing prospect that some patients exhibiting catatonia previously diagnosed as having encephalitis lethargica may have been suffering from an antibody-mediated encephalitis. (Dale et al., 2012)

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. (Murphy et al., 2015) The theory is that 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. (Leon et al., 2017) Antistreptococcal antibodies are often positive, (Swedo et al., 1998) although results of immunotherapy have been equivocal (Williams et al., 2016) and the status of PANDAS and PANS is currently subject to some controversy. (British Paediatric Neurology Association, 2021) A systematic review of treatments for PANS and PANDAS found four randomised controlled trials with very mixed results for antibiotics and immunotherapy. (Sigra et al., 2018) There has been one reported case of a boy who developed catatonic features in addition to obsessionality following infection with group A Streptococcus; he responded well to a combination of lorazepam and plasmapheresis. (Elia et al., 2005)

3.5.4 A model for autoimmunity in catatonia

In examining the role of the innate immune system, I 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. (Lancaster, 2016) In the specific case of NMDAR encephalitis, there is often little evidence of complement activation and neuronal degeneration. (Bauer and Bien, 2016) The fact that ketamine and phencyclidine – both NMDAR antagonists – trigger catatonia (Corlett et al., 2011) suggests that it is NMDAR antagonism that is responsible, the implication being that NMDAR encephalitis is more usefully understood as a synaptopathy. Genetic hypofunction of the NMDAR due to GRIN1 mutation also appears to predispose to psychosis (Tani et al., 2002), but the genetics of catatonia have not been established. Similarly, benzodiazepine withdrawal presents similarly to GABA-AR encephalitis. (Khan et al., 1980; Spatola et al., 2017)

Autoimmunity, therefore, may 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.

3.5.5 A model for glutamatergic hypofunction in catatonia

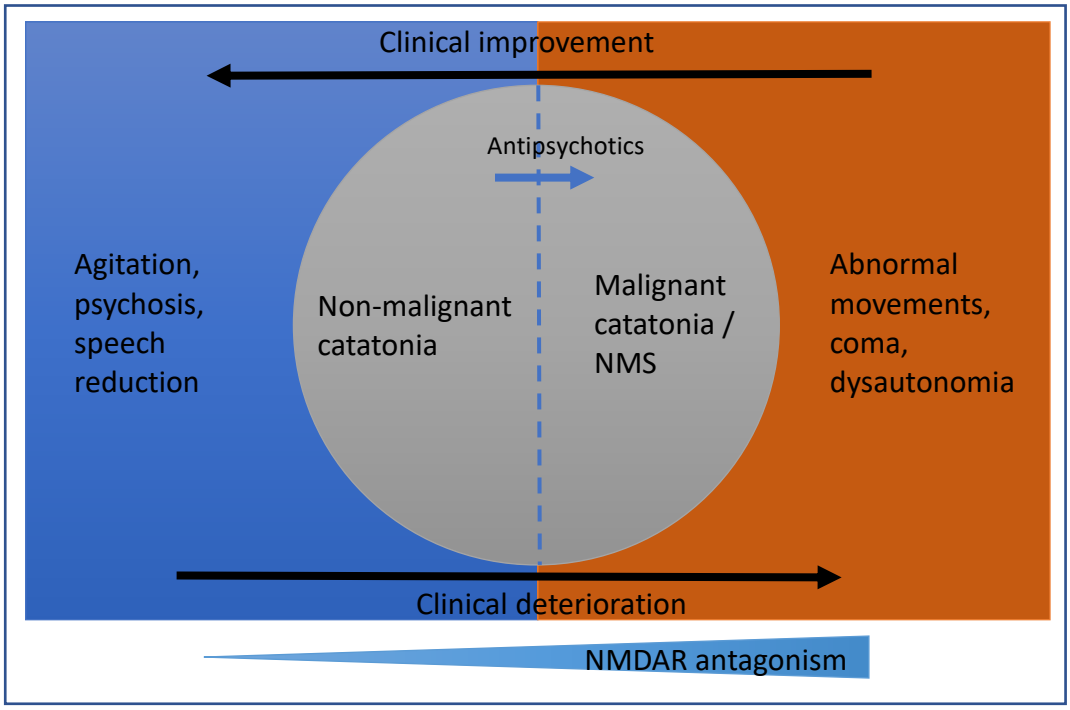
The close association between NMDAR encephalitis and catatonia may provide valuable insight into the pathophysiology of catatonia. NMDAR encephalitis causes internalisation of the NMDA receptor, resulting in a reversible reduction in the number of receptors and impaired AMPAR-mediated long-term potentiation. (Hughes et al., 2010; Jézéquel et al., 2017) This is consistent with catatonia also resulting from use of the recreational NMDA antagonists, ketamine and phencyclidine. (Corlett et al., 2011; Gouzoulis-Mayfrank et al., 2005)

To integrate findings of effective treatment with GABA-A receptor agonists and NMDAR antagonists, Northoff (2002) 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. 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. (Tang et al., 2006; Wu et al., 2005) 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 NMDA receptor is a post-synaptic receptor, but the neurons on which it is expressed may themselves be either excitatory glutamatergic neurons and inhibitory GABAergic neurons. (Inta et al., 2015) Moreover, both reduced and excessive NMDAR activity can result in neuronal apoptosis, (Chaves et al., 2018) but at physiological levels it can promote neuronal survival. (Papadia and Hardingham, 2007)

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, in neurological and autonomic dysfunction. (Dalmau et al., 2011) 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



3.6 Discussion

In this review of the literature, it has become evident that 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. It is reliant on cross-sectional studies that are unable to demonstrate temporal primacy, let alone causation. To give one example, it is quite possible that any peripheral inflammation in catatonia arises secondary to immobility and muscle breakdown. Moreover, studies did not tend to adjust for potential confounders. Examining the relationship of catatonia to the adaptive immune system reveals a strong and specific association with NMDAR encephalitis, which can be responsible for 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 I 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 at least some cases could be accounted for by autoimmune disorders such as NMDAR encephalitis.

Finally, is it possible to conclude whether catatonia is due to activation of the immune system? In many cases, the evidence is not currently compelling. However, where infection or autoimmunity are directed at certain specific targets in the CNS, there is a high risk of catatonia. Further investigations based on this concept may assist in elucidating the pathophysiology and improving the treatment of catatonia.

4 Demographic, clinical and laboratory associations of catatonia in a cohort and case-control study

This chapter has been previously published in an adapted form in Psychological Medicine. (Rogers et al., 2021)

4.1 Summary

4.1.1 Background

In this cohort study and case-control study, I characterise the demographic associations, peripheral inflammatory markers and outcome of catatonia, addressing Aims 1 and 2 of the thesis.

4.1.2 Methods

Electronic healthcare records were searched for validated clinical diagnoses of catatonia. In a case-control study, demographics and inflammatory markers were compared in psychiatric inpatients with and without catatonia. In a cohort study, the two groups were compared in terms of their duration of admission and mortality.

4.1.3 Results

I identified 1,456 patients with catatonia (of whom 25.1% had two or more episodes) and 24,956 other psychiatric inpatients. Incidence was 10.6 episodes of catatonia per 100,000 person-years. Patients with and without catatonia were similar in sex, younger and more likely to be of Black ethnicity. Serum iron was reduced in patients with catatonia (11.6 vs 14.2µmol/L, OR 0.65 [95% CI 0.45 to 0.95], p=0.03) and creatine kinase was raised (2545 vs 459 IU/L, OR 1.53 [95% CI 1.29 to 1.81], p<0.001), but there was no difference in C-reactive protein or white cell count. NMDA receptor antibodies were significantly associated with catatonia, but there were small numbers of positive results. Duration of hospitalisation was greater in the catatonia group (median 43 days vs 25 days), but there was no difference in mortality after adjustment.

4.1.4 Discussion

In this large clinical study of catatonia, I found catatonia occurred in approximately 1 per 10,000 person-years. Evidence for a proinflammatory state was mixed. Catatonia was associated with prolonged inpatient admission but not with increased mortality.

4.2 Background

To summarise the review of the literature in section 2.6, there is substantial uncertainty regarding the epidemiology of catatonia. Although a meta-analysis has estimated the prevalence of catatonia in various clinical samples, (Solmi et al., 2018) there are no reliable estimates of the incidence or prevalence of catatonia in the general population. Although there is some evidence for declining cases of catatonia in the 20th century, evidence in the 21st century is lacking and it has been contended that an apparent reduction in

incidence represents underdiagnosis. (Fink and Taylor, 2009) It is not even clear to what extent catatonia may be a relapsing and remitting disorder. Demographic studies to date have suggested that catatonia is more common in individuals of Black ethnicity, but there were methodological limitations in these studies. There is some work suggesting that catatonia confers a higher mortality compared to other psychiatric disorders, (Funayama et al., 2018; Niswander et al., 1963) but it requires modern methods and generalisation beyond schizophrenia.

As discussed at length in Chapter 3, more recent findings are posing questions about the immunology of catatonia. Notably, up to 88% of patients with *N*-methyl-*D*-aspartate (NMDA) receptor encephalitis exhibit catatonia at some point in their illness, (Dalmau et al., 2008) but it is unclear whether NMDA receptor autoantibodies are present at higher rates in patients with catatonia generally. Moreover, while several small studies have investigated serum iron, which initially appeared to be reduced in patients with catatonia, (Carrol and Goforth, 1995; Lee, 1998) small case-control studies have been equivocal. (Haouzir et al., 2009; Lakshmana et al., 2009; Peralta et al., 1999) Low serum iron has been found to be predictive of neuroleptic malignant syndrome and fever after antipsychotic administration in patients with catatonia. (Carrol and Goforth, 1995; Conca et al., 2003; Lee, 1998) Iron is a negative acute phase marker that is present at lower levels in acute inflammatory states and numerous autoimmune disorders have been reported with catatonia, so it may be a marker of an acute phase response in catatonia.

In this chapter, I address Aim 1 by characterising the neuroimmunology of catatonia. I build on Chapter 3, which addressed Objective 1.1. Specifically, my objective in this chapter is:

1.2 To compare clinical blood-based markers of inflammation and cell damage (C-reactive protein, iron, white cell count, creatine kinase and NMDA receptor antibodies) in psychiatric inpatients with and without catatonia in a case-control study using routinely collected electronic healthcare records. My hypothesis is that blood-based markers of inflammation and cell damage will provide more evidence of peripheral inflammation in catatonia.

In addition, I plan to address Aim 2 of the thesis by characterising the epidemiology of catatonia with the following specific objectives:

2.1 To estimate the population incidence of catatonia.

2.2 To compare the age, sex and ethnic groups of psychiatric inpatients with and without catatonia in a case-control study.

2.3 To compare the mortality and admission duration of psychiatric inpatients with and without catatonia in a cohort study. My hypothesis is that patients with catatonia have a higher mortality and admission duration.

4.3 Methods

4.3.1 Setting

The study used the Clinical Records Interactive Search (CRIS) system, run by the NIHR Maudsley Biomedical Research Centre, which is a large repository of anonymised electronic healthcare records from patients receiving care from the South London and Maudsley NHS Foundation Trust, UK. I selected this database for three reasons. Firstly, its size: This Trust is the largest unit provider of secondary mental health services in the UK, serving four London boroughs with a combined 2016 population of 1,317,000, as well as providing some specialist services to the UK population nationally. Unified electronic records were introduced between 2005 and 2006, importing previous electronic records dating to 1999. CRIS was developed in 2008 and incorporates these previous records as well as adding current records up to the present day. (Stewart et al., 2009) It currently contains records for over 500,000 individuals. The initial data extraction did not specify a time period in order to obtain the most expansive chronological data.

Secondly, there is a wide range of patients. Previous studies have often been limited to particular diagnostic groups (often catatonic schizophrenia) or settings (often psychiatric inpatients). CRIS allowed me to examine patients across settings as diverse as community teams, outpatient departments, psychiatric wards, a health-based place of safety and allied general hospitals. It also covers a range of diagnostic entities, including the full spectrum of psychiatric disorders as well as many patients with underlying medical problems.

Thirdly, a major advantage that CRIS has over many other large datasets used for epidemiological research is that it allows access to the unstructured free text fields. ICD-10 coding of catatonia is restricted to catatonic schizophrenia and organic catatonic disorder, necessarily omitting patients with catatonia secondary to other diagnoses and catatonia as a transitory feature in diagnoses such as paranoid schizophrenia. Using free text fields allowed me to include such cases and also to validate catatonia cases with reference to the clinical features present.

Data were initially extracted on 17/12/2018 with subsequent data extraction occurring on 24/01/2019, 04/02/2019, 17/12/2019 and 3/09/2021. The CRIS system has approval from the Oxfordshire C Research Ethics Committee (ref: 18/SC/0372) and this study was approved by the CRIS Oversight Committee (ref: 17-102).

4.3.2 Identifying patients with catatonia

To identify catatonia, I first applied a bespoke natural language processing algorithm for mentions of catatonia. The algorithm used the free text of clinical records, so it was able to detect mentions of catatonia that were not included in ICD-10 diagnoses, which are restricted to F06.1 – Organic catatonic disorder and F20.2 – Catatonic Schizophrenia. The algorithm had been developed against manually extracted gold

standard annotations to a performance level of 0.86 precision (positive predictive value) and 0.87 recall (sensitivity). (Jackson et al., 2017) One of three investigators (Jonathan Rogers, Nazifa Begum and Anna Griffin) examined each positive record retrieved by the algorithm to ensure that it met the following eligibility criteria:

1. A diagnosis of catatonia was made by a clinician for the patient in question. This excluded entries referring to a family history or catatonia merely listed on a differential diagnosis.
2. A date was given for the diagnosis of catatonia. This ensured that other variables such as age at diagnosis and treatment setting at time of diagnosis could be accurately ascertained.
3. There was clear evidence in the case record of at least two features of catatonia as defined by the Bush-Francis Catatonia Screening Instrument, a tool that has a high degree of interrater reliability, construct validity, sensitivity and specificity in the identification of catatonia. (Bush et al., 1996a, 1996b; Subramaniyam et al., 2020)

Where a patient had multiple episodes of catatonia, only one episode was required to list the catatonic features present. This decision was taken on the pragmatic grounds that often subsequent catatonic episodes were described as similar to prior episodes without giving details of the presentation.

To assess interrater reliability, thirty of the first patients' case notes were examined by more than one rater (10 by all three raters, 10 by Jonathan Rogers and Nazifa Begum, and 10 by Jonathan Rogers and Anna Griffin). Cohen's kappa coefficient for caseness on the Bush-Francis Catatonia Screening Instrument (BFCSI) was 0.68, which is considered 'substantial' agreement. (Landis and Koch, 1977)

4.3.3 Definition of variables

The derivation of demographic, clinical and laboratory characteristics is described in Table 9.

Table 9: Variable properties

Variable		**Structured field**	**NLP-derived**	**Free text analysed by researcher**	**Measurement**
Demographic	Age	●			For patients with catatonia, this was age at index date. For the comparison group, this was age on 1st June of the year they were admitted as an inpatient.
	Date of birth	●			Adjusted to first date of the month to preserve anonymisation
	Date of death	●			Linked to NHS Spine

	Ethnicity	●			Dichotomised as Black and not Black when used for adjustment in regression analyses
	Sex	●			As recorded on electronic healthcare record
	Index date	●			Date of admission to hospital
Diagnosis	Presence of catatonic features			●	According to Bush-Francis Catatonia Screening Instrument
	Diagnosis	●			Where an ICD-10 diagnosis had been coded prior to the index date, the most recent diagnostic code prior to the index date was used. Where there was no diagnostic code prior to the index, the earliest diagnostic code up to 6 months after the index date was used.
Treatment	Date of first referral accepted	●			First date on which a referral to the Trust was accepted
	Admission date	●			Date of admission to hospital
	Discharge date	●			Date of discharge from hospital
	Detention under the Mental Health Act	●			Included any active inpatient section from the index date until 2 weeks later
	Health of the Nation Outcomes Scale (HoNOS)	●			Latest before index date and earliest after index date.
Blood pressure	Systolic blood pressure		●		Earliest blood pressure within 2 weeks of index date
	Diastolic blood pressure		●		
Laboratory results	Full blood count	●			Earliest from index date to 14 days later
	Urea and electrolytes	●			
	Thyroid function and autoantibodies	●			
	Iron studies	●			
	Vitamin B12 and folate	●			
	Creatine kinase	●			
	D-dimer	●			
	Autoantibody profile	●			Earliest from index date to 1 year

4.3.4 Descriptive analysis

To maximise generalisability in terms of treatment setting, disease spectrum and time, all catatonia patients meeting the eligibility criteria above were included in the descriptive analyses. Descriptive statistics were used to investigate relapse and treatment settings. In order to assist with comparability with other studies, I also calculated the number of individuals who met DSM-5 criteria for catatonia. (American Psychiatric Association, 2013) Statistics are provided separately for adults and children.

To assess catatonia incidence, I divided the number of catatonic episodes among people resident in the catchment area by the population of the catchment area over the 10-year period for which full records were available (2007-2016). The population of the catchment area was based on the total of the populations of the four London boroughs of Southwark, Lambeth, Lewisham and Croydon, as reported by the UK Office for National Statistics. (Office for National Statistics, 2022)

In order to assess whether there was a change in catatonia incidence over time, this sample had to be modified slightly to prevent a reporting bias in which earlier catatonic episodes had a greater opportunity to be reported than later episodes (since some episodes were reported in retrospect). I therefore restricted the analysis to those patients with contemporaneously reported episodes of catatonia. Pearson's correlation was assessed between index year and number of contemporaneous cases. To further assess whether any change in case numbers was due to a change in the size of the catchment population, the same analysis was performed with the number of cases divided by the catchment population, as estimated by the UK Office for National Statistics. (Office for National Statistics, 2022)

4.3.5 Case-control study

My comparison group was drawn from the structured fields of electronic healthcare records and was composed of all individuals admitted to psychiatric wards within South London and Maudsley NHS Foundation Trust between 2007 and 2016, covering patients with a variety of diagnoses and ages, including services treating children, adults and older people. I included all psychiatric inpatients rather than restricting to any particular diagnostic group or age group because this reflected the diversity of the patients with catatonia. To ensure comparability of the two groups, patients with catatonia were included in these comparative analyses only if they were inpatients on psychiatric wards admitted between these dates.

Diagnoses (other than identification of catatonia) were made according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). (World Health Organization, 1992) Where more than one contemporaneous diagnosis was recorded, I reported the diagnosis designated as primary. I grouped diagnoses as organic disorders (ICD-10 codes F00-F09 and non-F codes); neurodevelopmental disorders (F70-89, F90 and F95); schizophrenia and related disorders (F20-F29); mood disorders (F30-F39); neurotic disorders (F40-59); personality and behavioural disorders (F50-69, F91-

F94, F98), and substance use disorders (F10-F19). I used this grouping because it represented a reasonable compromise between – on the one hand – distinguishing categories that might be likely to differ in terms of blood-based markers or mortality and – on the other hand – having a manageable number of groups for a categorical variable.

Analysis of laboratory markers was conducted in the Viapath Laboratory at King's College Hospital, apart from neuronal autoantibody analyses, which were conducted in the Oxford NHS Diagnostic Neuroimmunology Service. Serum NMDA receptor antibody level results (using the Oxford live cell-based assay prior to July 2015 and the Euroimmun fixed cell-based assay thereafter) (Oxford Diagnostic Immunology service, 2015) were officially reported by the laboratory as negative, weakly positive or positive. Because of evidence that weakly positive peripheral antibodies can be associated with autoimmune encephalitis and high titres in the CSF, (Cai et al., 2018; Qin et al., 2017) I grouped the weakly positive with the positive results to create two categories: negative and positive. Antibodies against the voltage-gated potassium channel, as measured by radioimmunoassay were reported, as data were collected prior to the reporting of antibodies to the LGI1 and CASPR2 antigens by the laboratory.

Age, sex, ethnicity, diagnostic group and laboratory markers were compared between patients with and without catatonia using logistic regression. Odds ratios for laboratory results were calculated unadjusted and adjusted for age, sex and Black ethnicity, as these demographic factors are known to affect the results of numerous laboratory tests. Where a high degree of positive skew was present in the laboratory results, natural logarithmic transformations were used; where zero values were present, a $\log_e(x+1)$ transformation was used. Where the odds ratios for laboratory results had very narrow confidence intervals, the results were divided by their standard deviations prior to transformation.

Due to missing data in the laboratory results, the number of cases for each individual result is reported. Associations with missing data were analysed. However, multiple imputation was not conducted because it is likely that – even with the use of all the available covariates – data are missing not at random (MNAR), as clinical factors (such as illness severity and medical complications) are likely to predict missingness and to be associated with the outcomes.

4.3.6 Cohort study

As in the case-control study, the comparison group was composed of all individuals admitted to psychiatric wards between 2007 and 2016. Patients with catatonia were included only if they were inpatients on psychiatric wards admitted between these dates. When analysing the duration of admission, patients with catatonia were included only where catatonia occurred within seven days of admission, to avoid a bias where catatonia becomes more likely due to patients spending longer in hospital. When analysing mortality, patients with catatonia were included only where catatonia was recorded within three days of its onset, to

avoid a survival bias in which only surviving patients would have the opportunity to have catatonia retrospectively recorded in their notes. Data were ascertained in the same way for patients with and without catatonia. Mortality data were obtained from linked national records as part of the NHS Spine. The time from index date to outcome (hospital discharge or death) was analysed using a Cox proportional baseline hazard model survival analysis, adjusting for age, sex, ethnicity and index year. An additional analysis adding diagnostic group as a covariate to the model was also conducted. The proportionality assumption was checked using visual inspection of the Kaplan-Meier plot.

4.3.7 Statistical analysis

Statistical analysis was conducted using Stata MP (version 15) with a threshold for statistical significance set to $p<0.05$. The manuscript was written according to STROBE recommendations and the STROBE Checklist is shown in Table 10. (von Elm et al., 2007)

Table 10: STROBE Checklist for study on epidemiology and inflammatory markers in catatonia

	Item No	**Recommendation**	**Location**
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4.1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2.4, 2.4, 4.2
Objectives	3	State specific objectives, including any prespecified hypotheses	4.2
Methods			
Study design	4	Present key elements of study design early in the paper	4.3.4, 4.3.5, 4.3.6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4.3.1, 4.3.2
Participants	6	*Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	4.3.2, 4.3.4, 4.3.5, 4.3.6

		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4.3.2, 4.3.3, 4.3.4, 4.3.5, 4.3.6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4.3.2, 4.3.3, 4.3.4, 4.3.5, 4.3.6
Bias	9	Describe any efforts to address potential sources of bias	4.3.6, 4.3.7
Study size	10	Explain how the study size was arrived at	4.3.2, Figure 2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4.3.2, 4.3.3, 4.3.4, 4.3.5, 4.3.6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4.3.2, 4.3.4, 4.3.5, 4.3.6, 4.3.7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
	I) Explain how missing data were addressed		4.3.5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	4.3.6
	I) Describe any sensitivity analyses		4.3.6

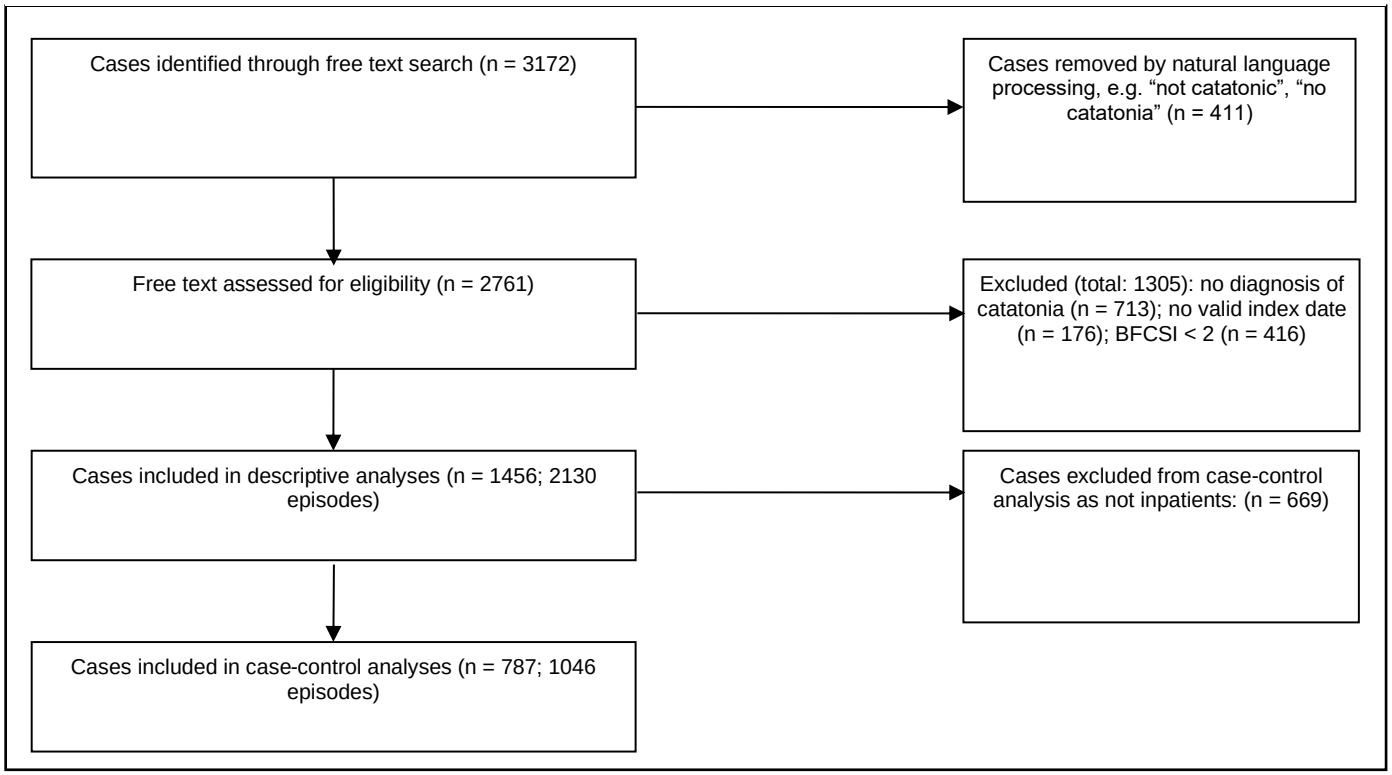
4.4 Results

4.4.1 Occurrence

The sample consisted of 2,130 episodes of catatonia in 1,456 subjects, as shown in Figure 2. Overall, in the 10-year period from 2007 to 2016, among patients who were resident in the healthcare provider's catchment

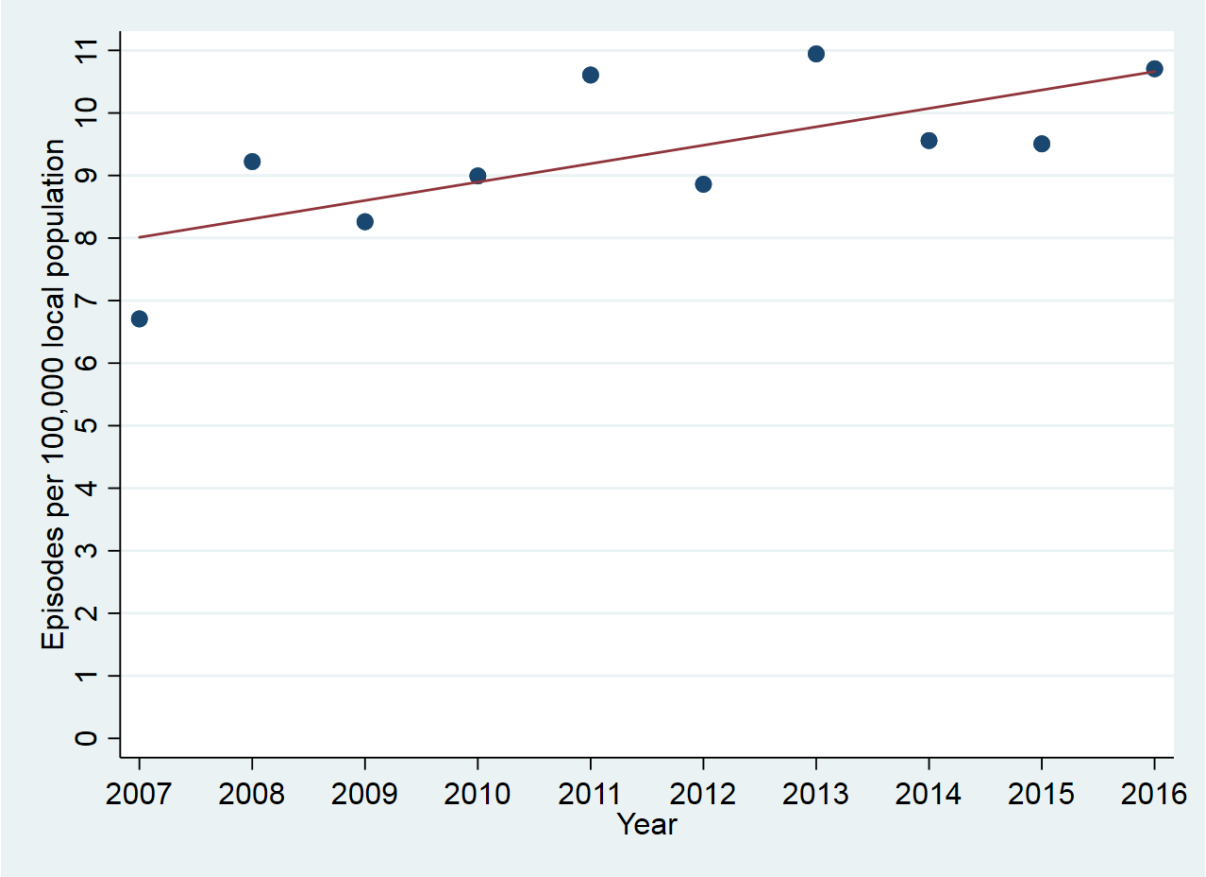
area, there were 1,316 episodes of catatonia (852 unique patients) for the provider's total catchment of 1,242,055, giving an incidence of 10.6 (95% CI 10.0 to 11.1) episodes per 100,000 person-years. Where the more stringent DSM-5 criteria were used, there were 901 episodes of catatonia in 586 individuals. Among

Figure 2: Identification and screening of cases. BFCSI – Bush-Francis Catatonia Screening Instrument



adults, there were 1,214 episodes of catatonia in a mean population of 968,064, giving an incidence of 12.5 (95% CI 11.8 to 13.3) episodes per 100,000 person-years. Among children, there were 102 episodes of catatonia in a mean population of 273,990, giving an incidence of 3.7 (95% CI 3.0 to 4.5) episodes per 100,000 person-years. Examining only those episodes that were contemporaneously reported between 2007 and 2016, there was a positive correlation between index year and number of episodes (r=0.70, p=0.02), as shown in Figure 3. This remained after adjusting for the mean age of the population each year (r=0.71, p=0.03).

Figure 3: Contemporaneously recorded catatonic episodes per 100,000 local population by year



Number of episodes per patient ranged between 1 and 27 (mean 1.5, SD 1.2, median 1, IQR 1 – 2) over a mean follow-up time of 7.0 years (SD 5.1 years). After the first episode, subsequent episodes occurred at a rate of 0.035 episodes (SD 0.086) per year with 25.1% experiencing at least two episodes within the follow-up period. However, after five episodes, further episodes occurred in 55.9%.

The age range for the patients at the time of first recorded diagnosis of catatonia was between 5 and 91 years (mean 35.4, median 32, SD 16.2, IQR 23 – 45 years). In terms of treatment setting at the time of diagnosis of catatonia, 1046 episodes (49.1%) were diagnosed when the individual was an inpatient on a psychiatric ward, 462 (21.7%) were in a community mental health team, 217 (10.2%) were in a general hospital, 54 (2.5%) were in a crisis resolution and home treatment team, 28 (1.3%) were in a health-based place of safety and in 323 (15.2%) the treatment setting was not specified. 1022 (48.0%) were detained under the Mental Health Act for compulsory treatment within two weeks of the index date. The mean number of features of the BFCSI present was 3.6 (SD 1.7). Patients with adult and paediatric first presentation of catatonia are compared in Table 11.

Table 11: Comparison of demographic and clinical data for adult and paediatric patients with catatonia

		Paediatric presentation (1st episode at <18 years)	Adult presentation (1st episode ≥18 years)	Total sample
	Number of patients	119	1,337	1,456
	Number of episodes	203	1,927	2,130
	Number of episodes per patient, median (IQR)	1 (1 to 2)	1 (1 to 1)	1 (1 – 2)
	Number of episodes per patient, mean (SD)	1.7 (2.6)	1.4 (1.0)	1.5 (1.2)
Figures provided per patient (first episode)	**Age at first episode, mean (SD)**	14.6 (2.7)	37.3 (15.6)	35.4 (16.2)
	Age at first episode, median (range, IQR)	15 (5 to 17; 14 to 17)	34 (18 to 91; 25 to 46)	32 (5 to 91; 23 to 45)
	Sex (*n*, %)			
	- Male	77 (64.7)	726 (54.3)	803 (55.2)
	- Female	42 (35.3)	611 (45.7)	653 (44.9)
	Ethnicity (*n*, %)			
	- White	28 (23.5)	469 (35.1)	497 (34.1)
	- Asian / Asian British	12 (10.1)	81 (6.1)	93 (6.4)
	- Black / African / Caribbean / Black British	55 (46.2)	646 (48.3)	701 (48.1)
	- Mixed / Multiple ethnic groups	10 (8.4)	39 (2.9)	49 (3.4)
	- Other ethnic groups	10 (8.4)	77 (5.8)	87 (6.0)
	- Not stated	4 (3.4)	25 (1.9)	29 (2.0)
	BFCSI score, median (IQR)	3 (2-5)	3 (2-4)	3 (2-5)
	BFCSI score, mean (SD)	3.9 (1.9)	3.6 (1.7)	3.6 (1.7)
Figures provided per episode	**Treatment setting (*n*, %)**			
	- Psychiatric ward	69 (34.0)	977 (50.7)	1,046 (49.1)
	- Community mental health team	72 (35.5)	390 (20.2)	462 (21.7)
	- General hospital	11 (5.4)	206 (10.7)	217 (10.2)
	- Crisis resolution and home treatment team	2 (1.0)	52 (2.7)	54 (2.5)
	- Health-based place of safety	0 (0.0)	28 (1.5)	28 (1.3)
	- Not specified	49 (24.1)	274 (14.2)	323 (15.2)

	Detention under Mental Health Act for compulsory treatment within 2 weeks of index date (*n*, %)			
	- Detained	58 (28.6)	964 (50.0)	1,022 (48.0)
	- Not detained	145 (71.4)	963 (50.0)	1,108 (52.0)

4.4.2 Case-control study

The comparison group was drawn from all inpatients admitted to the Trust between 2007 and 2016 and represented 24,956 patients with 37,456 inpatient episodes. Demographic comparisons are made in Table 12. Patients with catatonia were similar to the control group in sex ratio but younger and more likely to be from an ethnic minority background. There were significant differences in the underlying diagnoses of the two groups.

Table 12: Characteristics of groups: odds ratio for catatonia according to age, sex, ethnicity and diagnosis.

	Inpatients with catatonia (*n*=787)	**Control patients (*n*=24,956)**	**Unadjusted analysis**		**Adjusted analysis [a]**	
			OR (95% CI)	*p*	aOR (95% CI)	*p*
Total number of episodes	1046	37,456	-	-	-	-
Age in years at first episode, mean (SD) [b]	37.0 (15.8)	40.0 (17.1)	**0.91 (0.87 to 0.95)**	**<0.001**	-	
Age in years at first episode, median (range, IQR)	34 (9 to 91; 24 to 46)	37 (5 to 100; 27 to 49)	**-**	**-**	-	-
Age < 18 at index episode, *n* (%)	41 (5.2)	1835 (7.4)	**0.69 (0.50 to 0.95)**	**0.02**	-	-
Sex, *n* (%)						
- **Female**	362 (46.0%)	11,457 (45.9%)	1 (reference)	-	1 (reference)	-
- **Male**	425 (54.0%)	13,495 (54.1%)	0.997 (0.864 to 1.15)	0.96	-	-
- **Not stated**	0 (0.0%)	4 (0.02%)	-	-	-	-
Ethnicity (%)						
- **White**	233 (29.6%)	15,340 (61.5%)	1 (reference)	-	1 (reference)	-
- **Asian / Asian British**	54 (6.9%)	1291 (5.2%)	**2.75 (2.04 to 3.72)**	**<0.001**	**2.68 (1.98 to 3.63)**	**<0.001**

- **Black / African / Caribbean / Black British**	421 (53.5%)	6,115 (24.5%)	**4.53 (3.85 to 5.33)**	**<0.001**	**4.45 (3.78 to 5.24)**	**<0.001**
- **Mixed / Multiple ethnic groups**	29 (3.7%)	609 (2.4%)	**3.14 (2.11 to 4.65)**	**<0.001**	**2.99 (2.01 to 4.44)**	**<0.001**
- **Other ethnic groups**	47 (6.0%)	1,237 (5.0%)	**2.50 (1.82 to 3.44)**	**<0.001**	**2.43 (1.77 to 3.35)**	**<0.001**
- **Not stated**	3 (0.4%)	364 (1.5%)	-	-	-	-
Diagnostic group at first episode (%)						
- **Organic disorders**	21 (2.7%)	1332 (5.3%)	**0.20 (0.13 to 0.32)**	**<0.001**	**0.32 (0.20 to 0.51)**	**<0.001**
- **Neurodevelopmental disorders**	16 (2.0%)	546 (2.2%)	**0.24 (0.11 to 0.52)**	**<0.001**	**0.29 (0.13 to 0.62)**	**0.001**
- **Schizophrenia and related disorders**	456 (57.9%)	5866 (23.5%)	1 (reference)	-	1 (reference)	-
- **Mood disorders**	154 (19.6%)	5342 (21.4%)	**0.37 (0.31 to 0.45)**	**<0.001**	**0.47 (0.39 to 0.57)**	**<0.001**
- **Neurotic disorders**	32 (4.1%)	2433 (9.7%)	**0.17 (0.12 to 0.24)**	**<0.001**	**0.22 (0.15 to 0.32)**	**<0.001**
- **Personality and behavioural disorders**	18 (2.3%)	1673 (6.7%)	**0.14 (0.09 to 0.22)**	**<0.001**	**0.18 (0.11 to 0.29)**	**<0.001**
- **Substance use disorders**	15 (1.9%)	4361 (17.5%)	**0.04 (0.03 to 0.07)**	**<0.001**	**0.06 (0.03 to 0.10)**	**<0.001**
- **Not stated**	75 (9.5%)	3403 (13.6%)	-	-	-	-

[a] Ethnicity adjusted for age and sex. Diagnostic group adjusted for age, sex and Black ethnicity. [b] ORs calculated using age in decades.

The main laboratory test results are compared in Table 13 with additional exploratory outcomes presented in Table 14. As an additional exploratory analysis, I investigated whether serum iron and creatinine kinase were altered at baseline, or whether there was a change that corresponded to the onset of catatonia. I included all patients with catatonia who had laboratory results both for a catatonic episode and that was at least one month from any catatonic episode. Paired *t*-tests were then used to compare the result from when the patient had catatonia with the average of the non-catatonic results. No statistically significant differences were detected between creatine kinase or iron at baseline compared to during an episode of catatonia, but numbers were small (see Table 15). Comparing selected laboratory test results between patients in the catatonia group who did and did not have low serum iron revealed no significant differences after adjustment (see Table 16). I also explored whether the high creatine kinase within the catatonia group was related to muscular rigidity or to rhabdomyolysis due to immobility by testing the associations between creatine kinase and each of rigidity and immobility. I found no significant relationship between creatine kinase and either of these clinical features, either in a univariable or multivariable analysis, as shown in Table 17. When receiver

operating characteristic (ROC) analysis was conducted for CK and catatonia diagnosis, the area under the curve (AUC) was 0.64, as shown in Figure 4.

Table 13: Laboratory results for patients with catatonia and the control group, presenting mean levels and odds ratios for catatonia according to laboratory test level

Test	**Patients with catatonia (*n*=787)**		**Control patients (*n*=24,955)**		**Unadjusted analysis**		**Adjusted analysis [a]**	
	n	Mean (+/- SD)	*n*	Mean (+/- SD)	OR (95% CI)	*p*	aOR (95% CI)	*p*
Iron (µmol/L) [b]	46	11.6 (5.2)	1655	14.2 (7.9)	**0.65 (0.45 to 0.95)**	**0.03**	**0.65 (0.44 to 0.97)**	**0.04**
Creatine kinase (IU/L) [c]	74	5.87 (1.42) *2545*	1881	5.20 (1.09) *459*	**1.53 (1.29 to 1.81)**	**<0.001**	**1.52 (1.27 to 1.83)**	**<0.001**
White cell count (10^9/L) [b]	195	7.15 (2.65)	8719	7.21 (2.68)	0.98 (0.84 to 1.13)	0.76	1.05 (0.91 to 1.21)	0.68
C-reactive protein (mg/L) [c]	147	1.49 (1.07) *9.1*	5253	1.37 (0.98) *7.9*	1.13 (0.97 to 1.32)	0.13	1.14 (0.98 to 1.34)	0.10
NMDA receptor antibodies	54	Positive in 3	481	Positive in 5	**5.6 (1.3 to 24.1)**	**0.02**	**6.2 (1.4 to 27.3)**	**0.02**

[a]Adjusted for age, sex and ethnicity. [b] Due to very small confidence intervals, these odds ratios have been calculated by dividing the laboratory result by its standard deviation. [c] Due to positive skew, these results underwent a natural logarithm transformation. Log_e results are in normal text with original results in italics (analyses performed using log_e results)

Table 14: Additional exploratory laboratory results for patients with and without catatonia

Test	**Patients with catatonia (n=787)**		**Control patients (n=24,956)**		**Unadjusted analysis**		**Adjusted analysis [a]**	
	n	Mean (+/- SD)	*n*	Mean (+/- SD)	OR (95% CI)	*p*	aOR (95% CI)	*p*
Erythrocyte sedimentation rate (mm/hr) [b]	28	14.1 (11.9)	1146	14.8 (18.4)	0.96 (0.65 to 1.42)	0.84	0.87 (0.55 to 1.37)	0.54
Full blood count								
- Haemoglobin (g/L) [b]	195	134 (16)	8723	137 (16)	**0.82 (0.72 to 0.94)**	**0.004**	0.93 (0.79 to 1.09)	0.35
- Mean corpuscular volume (fL) [b]	195	88.6 (7.3)	8723	91.2 (7.1)	**0.71 (0.62 to 0.81)**	**<0.001**	**0.76 (0.66 to 0.87)**	**<0.001**

-	Neutrophil count (10^9/L) [b]	195	4.69 (2.38)	8719	4.49 (2.15)	1.09 (0.95 to 1.24)	0.22	**1.18 (1.04 to 1.34)**	**0.01**
-	Lymphocyte count (10^9/L)	195	1.86 (0.70)	8719	2.05 (1.03)	**0.70 (0.57 to 0.86)**	**0.001**	**0.67 (0.54 to 0.83)**	**<0.001**
-	Monocyte count (10^9/L)	195	0.46 (0.19)	8719	0.46 (0.19)	0.89 (0.41 to 1.92)	0.77	1.31 (0.61 to 2.81)	0.50
-	Eosinophil count (10^9/L) [b]	195	0.12 (0.09)	8717	0.17 (0.16)	**0.58 (0.46 to 0.73)**	**<0.001**	**0.61 (0.48 to 0.77)**	**<0.001**
-	Basophil count (10^9/L) [b]	195	0.032 (0.020)	8705	0.038 (0.024)	**0.73 (0.60 to 0.87)**	**0.001**	**0.79 (0.66 to 0.95)**	**0.012**
-	Platelets (10^9/L) [b]	195	266 (78)	8723	262 (87)	1.05 (0.91 to 1.20)	0.52	1.02 (0.89 to 1.18)	0.74
-	Neutrophil-lymphocyte ratio	195	3.0 (2.6)	8719	2.5 (1.6)	**1.13 (1.07 to 1.19)**	**<0.001**	**1.16 (1.10 to 1.23)**	**<0.001**
-	Monocyte-lymphocyte ratio	195	0.27 (0.14)	8719	0.25 (0.12)	**3.47 (1.45 to 8.30)**	**0.005**	**6.02 (2.54 to 14.2)**	**<0.001**
-	Platelet-lymphocyte ratio [b]	195	163 (83)	8719	144 (72)	**1.21 (1.09 to 1.34)**	**<0.001**	**1.22 (1.10 to 1.36)**	**<0.001**
Thyroid function									
-	Free T_4 (pmol/L) [b]	140	15.9 (3.37)	8027	14.8 (3.0)	**1.20 (1.08 to 1.34)**	**0.001**	**1.20 (1.06 to 1.35)**	**0.003**
-	Thyroid stimulating hormone (mIU/L) [c]	140	0.84 (0.54) *2.0*	7953	0.90 (0.42) *1.8*	0.69 (0.44 to 1.07)	0.10	0.74 (0.48 to 1.15)	0.18
Haematinics									
-	Ferritin (µg/L) [c]	96	4.41 (1.10) *135*	4588	4.33 (1.04) *137*	1.08 (0.89 to 1.31)	0.44	1.16 (0.94 to 1.44)	0.16
-	Vitamin B12 (ng/L) [b]	120	553 (291)	6959	498 (258)	**1.19 (1.03 to 1.37)**	**0.02**	1.11 (0.95 to 1.29)	0.20

- Folate (µg/L) [b]	117	8.8 (6.1)	6624	8.8 (5.6)	1.02 (0.85 to 1.22)	0.86	1.01 (0.84 to 1.21)	0.92
Albumin (g/L)	188	43.4 (4.0)	7978	43.9 (3.7)	0.97 (0.93 to 1.00)	0.09	0.99 (0.95 to 1.03)	0.48
Creatinine (µmol/L)	192	77.7 (46.3)	8030	74.0 (39.2)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)		
'Voltage-gated potassium channel' antibodies (pM/L) [c]	42	1.73 (1.92) *73*	389	1.05 (1.73) 1.06 *37*	0.90 (0.74 to 1.09)	0.27	0.88 (0.73 to 1.08)	0.23

[a]Adjusted for age, sex and ethnicity. [b] Due to very small confidence intervals, these odds ratios have been calculated by dividing the laboratory result by its standard deviation. [c] Due to positive skew, these results underwent a natural logarithm transformation. Log_e results are in normal text with original results in italics (analyses performed using log_e results)

Table 15: Longitudinal comparison of creatine kinase and iron in patients with catatonia

Laboratory result	***n***	**Result when catatonia present, mean (+/- SD)**	**Result when catatonia not present (+/- SD)**	**Mean difference (95% CI)**	***p***
Creatine kinase (µmol/L) [a]	20	6.3 (1.7)	5.6 (1.1)	0.7 (-0.1 to 1.5)	0.08
Iron (µmol/L)	15	9.5 (3.5)	11.9 (4.6)	-2.4 (-5.4 to 0.6)	0.11

[a] Due to positive skew, creatine kinase results underwent a natural logarithm transformation.

Table 16: Comparison of patients with catatonia with and without low serum iron

	Serum iron low (*n=33)*		**Serum iron normal or high (*n=13)***		**Unadjusted analysis**		**Adjusted analysis [a]**	
	n	**Mean (+/-SD)**	***n***	**Mean (+/-SD)**	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Haemoglobin (g/L)	32	130 (16)	12	139 (20)	0.97 (0.93 to 1.01)	0.14	1.00 (0.95 to 1.06)	0.92
White cell count (10^9/L)	32	7.0 (2.4)	12	6.8 (2.4)	1.0 (0.8 to 1.4)	0.85	1.1 (0.7 to 1.7)	0.63

C-reactive protein (mg/L) [b]	28	1.7 (1.2) *11*	9	1.1 (0.8) *5*	1.8 (0.7 to 4.3)	0.22	1.3 (0.5 to 3.5)	0.58
Erythrocyte sedimentation rate (mm/hr)	5	19 (11)	4	14 (16)	1.0 (0.9 to 1.2)	0.50	0.6 (0.1 to 2.0)	0.41
Ferritin (µg/L) [b]	32	4.6 (1.0) *168*	11	4.6 (1.0) *129*	1.0 (0.5 to 2.1)	0.92	2.0 (0.6 to 6.7)	0.25
Albumin (g/L)	33	43 (3)	12	46 (4)	0.75 (0.58 to 0.96)	0.03	0.87 (0.65 to 1.15)	0.32
NMDA receptor antibodies	6	Negative in 6	1	Negative in 1	-	-	-	-

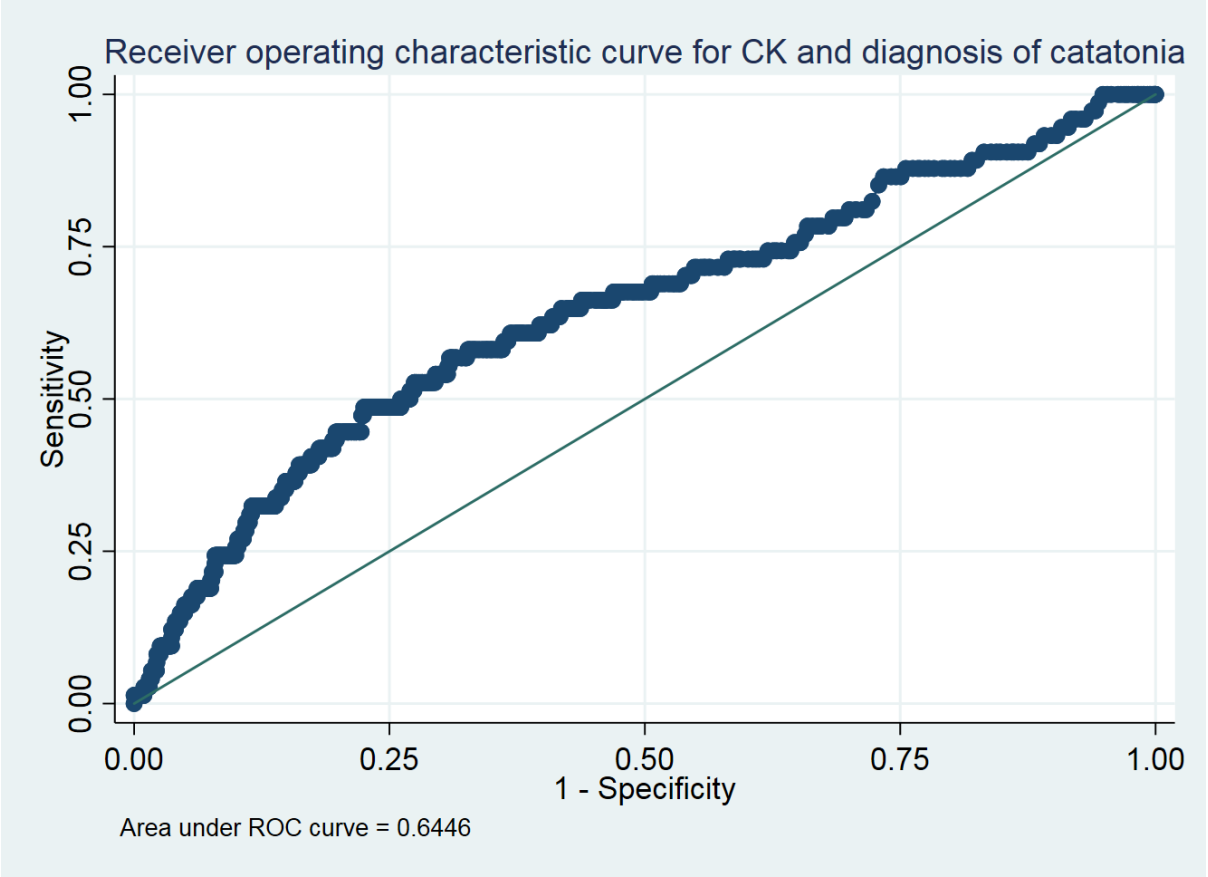
[a] Adjusted for age, sex and Black ethnicity. [b] Due to positive skew, these results underwent a natural logarithm transformation. Log_e results are in normal text with original results in italics (analyses performed using log_e results)

Table 17: Association of creatine kinase with rigidity and immobility

Creatine kinase (IU/L) [a]	**Patients with catatonia (n=787)**		**Unadjusted analysis**		**Adjusted analysis** [b]	
	n	Mean (+/- SD)	OR (95% CI)	*p*	aOR (95% CI)	*p*
Rigidity						0.30
- **Present**	20	5.66	0.86 (0.58 to 1.27)	0.45	0.80 (0.53 to 1.22)	
- **Absent**	54	5.94				
Immobility / stupor						
- **Present**	51	5.82	0.92 (0.66 to 1.30)	0.66	0.95 (0.66 to 1.35)	0.76
- **Absent**	23	5.98				

[a] Due to positive skew, creatine kinase underwent a natural logarithm transformation. [b] Adjusted for age, sex and ethnicity.

Figure 4: Receiver operating characteristic curve for CK and diagnosis of catatonia



In terms of missing data, three valid laboratory values were present for 9.1% of the inpatient episodes with catatonia and 6.3% of the inpatient control episodes. When the missing data were analysed, there were significant associations between having missing data with catatonic group membership, age, sex and Black ethnicity, but the absolute differences were very small. Associations are shown in Table 18.

Table 18: Comparison of associations with missing and non-missing data (as measured by inpatients having 3 or more valid laboratory test results)

		***n* (%) missing**		***n* (%) missing**	***p***
Sex	Male	19,646 (94.2)	Female	16,404 (93.0)	<0.001
Ethnicity	Black	10,675 (93.2)	Not Black	25,046 (93.9%)	0.009
Group	Catatonia	951 (90.9)	Comparison	35,103 (93.7)	<0.001
		***n* (%) missing**	**Mean (+/-) SD for missing**	**Mean (+/-) SD for not missing**	***p***
Age (years)		36,051 (93.6)	40.1 (16.2)	39.1 (16.5)	0.002

4.4.3 Cohort study

When I compared the 556 episodes of catatonia (473 patients) recognised within 7 days of admission with the control group using survival analysis with hospital discharge as the outcome, I found that the baseline proportional hazards assumption was reasonable (see Kaplan-Meier plots in Figure 5 and Figure 6). The median duration of inpatient stay was 43 days (95% CI 40 to 49 days) among patients with catatonia, compared to 25 days (95% CI 25 to 26 days) in the comparison group. The unadjusted Cox proportional hazard ratio (HR) for hospital discharge was 0.77 (95% CI 0.71 to 0.84, p<0.001); after adjusting for age, sex, Black ethnicity and year of admission, it was 0.78 (95% CI 0.72 to 0.85, p<0.001). After the addition of diagnostic group as a covariate to the model, the HR was 0.83 (95% CI 0.76 to 0.90, p<0.001). When the analysis was restricted to those subjects with a first episode in adulthood, the results were similar (unadjusted HR 0.77 [95% CI 0.70 to 0.83], p<0.001; adjusted HR 0.76 [95% CI 0.69 to 0.83], p<0.001).

Figure 5: Unadjusted Kaplan-Meier curve for hospital discharge

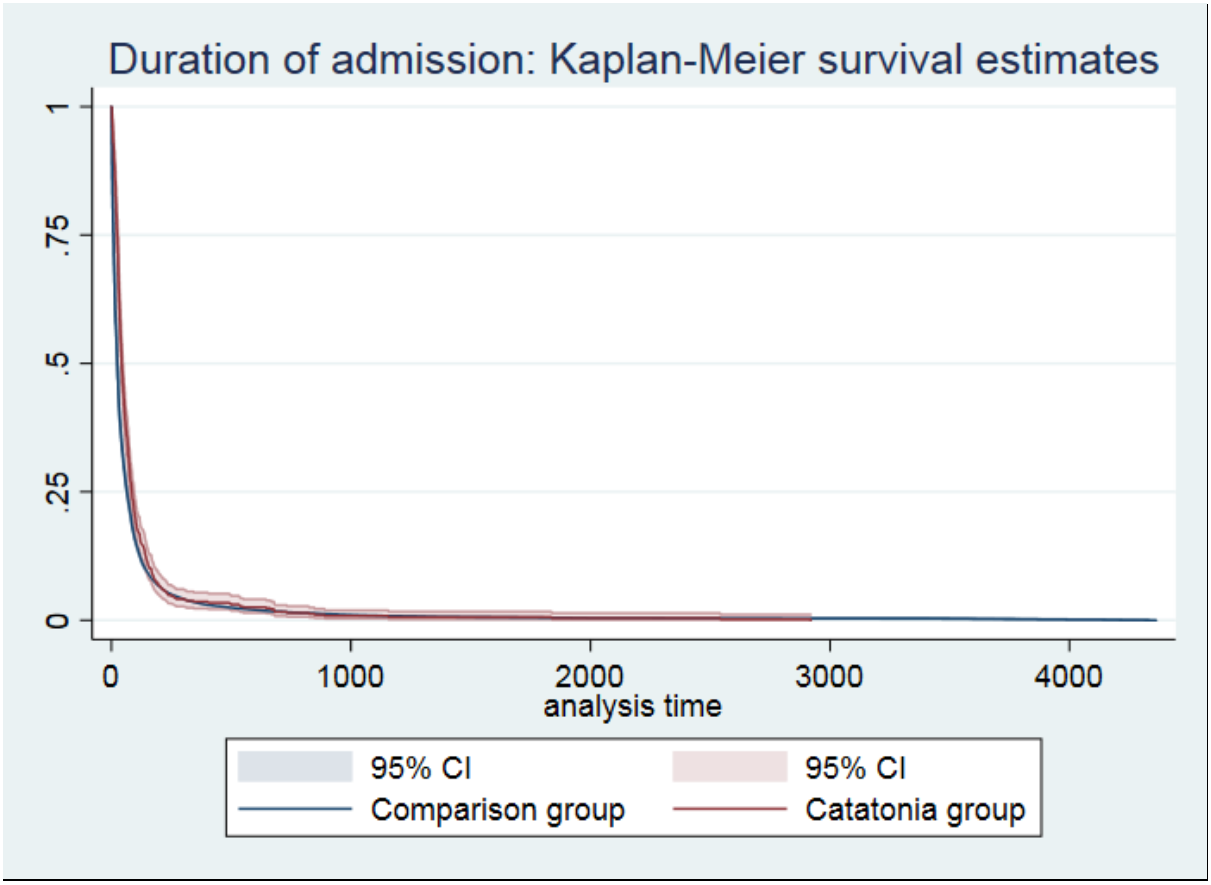
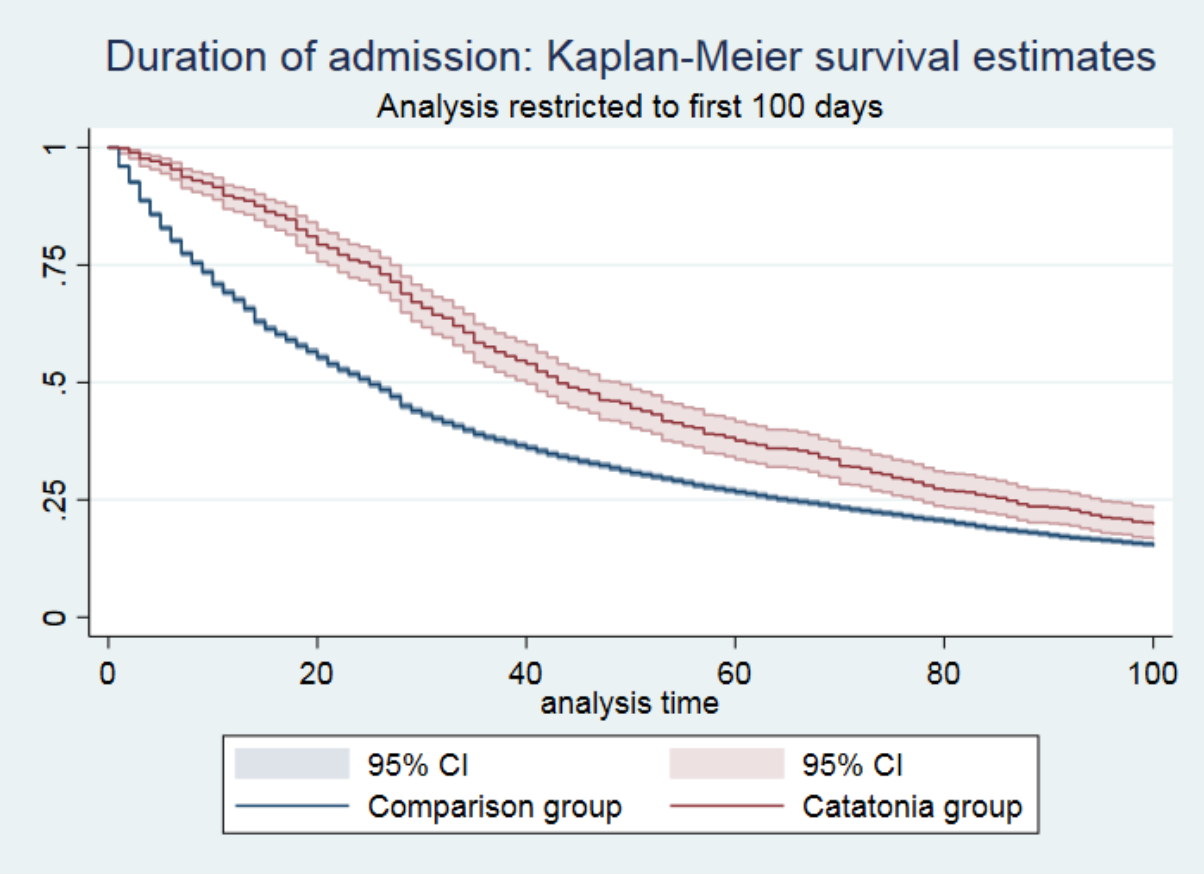
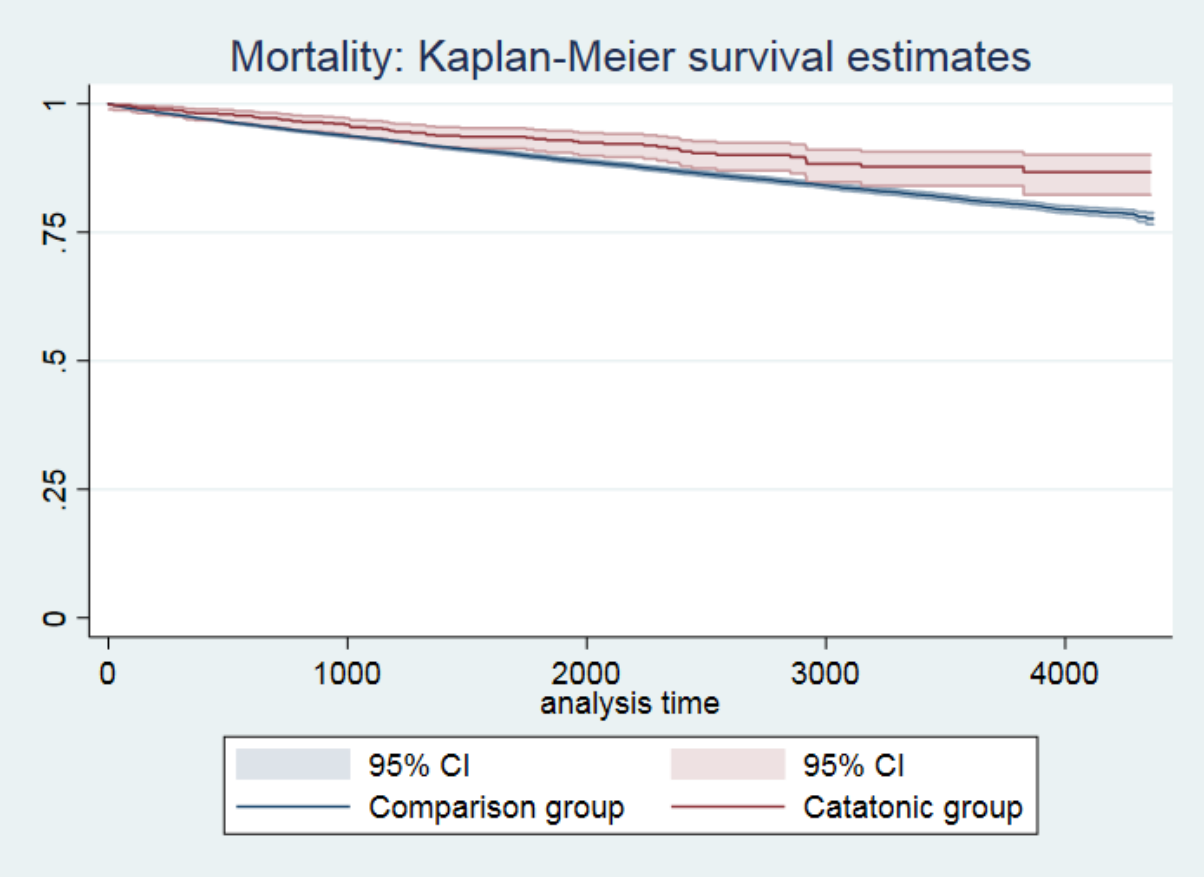


Figure 6: Unadjusted Kaplan-Meier curve for hospital discharge restricted to first 100 days



When I compared the 646 patients with catatonia recorded within 3 days of its occurrence with the control group with mortality as the outcome, I found that the baseline proportional hazards assumption was reasonable (see Kaplan-Meier plot in Figure 7). 3,535 deaths (58 in the catatonia group) occurred during a mean follow-up time of 7.0 years (SD 3.2). While there was a lower mortality among patients with catatonia in the unadjusted analysis (HR 0.66 [95% CI 0.51 to 0.85], *p*=0.001), after adjustment for age, sex, Black ethnicity and year of admission, there was no evidence for a difference between patients with and without catatonia (adjusted HR = 0.93 [95% CI 0.72 to 1.21], *p*=0.60). After the addition of diagnostic group as a covariate to the model, the HR was 1.12 (95% CI 0.86 to 1.45, *p*=0.42). When the analysis was restricted to those subjects with a first episode in adulthood, the results were similar (unadjusted HR 0.64 [95% CI 0.49 to 0.83], *p*=0.001; adjusted HR 0.92 [95% CI 0.71 to 1.20], *p*=0.54).

Figure 7: Unadjusted Kaplan-Meier curve for mortality



4.5 Discussion

This study used data from electronic patient records and was at the time it was first published, to my knowledge, the largest clinical study on catatonia published to date. (Solmi et al., 2018) My results show that patients diagnosed with catatonia had a similar sex ratio to the general population of psychiatric inpatients, but those with catatonia were slightly younger. There was a considerable difference in ethnicity between the two groups with Black patients being substantially overrepresented among those with recorded catatonia. It has previously been proposed that this disparity is due to different interpretation of symptoms by clinicians of the dominant culture. (Hutchinson et al., 1999) Other possible explanations include cultural differences in illness expression and genetic factors. It has been reported that schizophrenia is more common among migrant populations, (Saha et al., 2005) but I found that the overrepresentation of schizophrenia in this catatonia population did not fully explain the ethnicity differential. Non-European origin has been shown to be a risk factor for tardive dyskinesia, another movement disorder commonly seen in psychiatric practice. (Tenback et al., 2009)

Mahendra (1981) famously hypothesised, based on clinical experience, that catatonia was becoming less common. In this study, I found increasing annual numbers of patients with catatonia between 2007 and 2016. Apart from increased recognition, one possible reason for an increase in catatonia diagnosis would be the use of certain novel psychoactive drugs (such as synthetic cannabinoids, synthetic cathinones and phenethylamines), (Mdege et al., 2017) some of which have been linked to catatonia (Khan et al., 2016; Richman et al., 2018). I have since investigated this question in the current dataset: the number of substance-related catatonic episodes did increase between 2007 and 2016, but it still accounted for a small proportion of all catatonic episodes, so it may not be the only explanation for the growing incidence. (Yeoh et al., 2022). The overall incidence of catatonia that I calculated (10.6 episodes per 100,000 person-years) is somewhat lower than a previous US estimate of 33.0 per 100,000 person-years, which inferred incidence of catatonia indirectly using proportions reported in other diagnoses. (Taylor and Fink, 2003) My figures likely represent an underestimate of the true incidence of catatonia, given that most cases of catatonia are not recognised by clinicians and catatonic signs are poorly identified. (Takács et al., 2021; van der Heijden et al., 2005) This may be particularly the case in a general hospital, where catatonia has been found to be common among critically ill patients; (Grover et al., 2014; Wilson et al., 2017) it is possible that such patients did not come to the attention of a psychiatric team.

The diagnostic heterogeneity of catatonia in my study differed somewhat from other studies in that schizophrenia and related disorders, rather than mood disorders, were most common. (Taylor and Fink, 2003) It is likely that my data represent overdiagnosis of schizophrenia, as a relic of the Kraepelinian concept of catatonia as existing purely as a subtype of schizophrenia. (Shorter and Fink, 2018) According to one survey of psychiatrists, most clinicians still view catatonia as residing within the framework of schizophrenia. (Takács et al., 2021) In addition, the diagnostic coding used is still ICD-10, which only formally recognises catatonia in the context of F20.2 – Catatonic schizophrenia and F06.1 – Organic catatonic disorder. My data show that, although approximately half of cases of catatonia are recognised on psychiatric wards, appreciable numbers of diagnoses occur in other treatment settings, such as in community teams and general hospitals. However, my data are limited to patients presenting to psychiatric services and it is likely that many cases present in general hospitals and are not assessed by a psychiatrist. I should note that I report the treatment setting and whether patients were detained at the point at which catatonia was recognised, so it is possible that many patients were admitted to psychiatric hospitals shortly after catatonia recognition.

My data on catatonia relapse show that for three quarters of patients with a first reported catatonic episode, during an average follow-up period of 7.0 years, there were no further episodes. However, there was evidence to suggest that in patients with multiple episodes, the probability of relapse is

much higher, providing some evidence for Gjessing's description of periodic catatonia. (Gjessing, 1932) Relapse was more common in those with an underlying psychotic disorder, although this may reflect an understanding that individuals with relapsing catatonia must necessarily be suffering from catatonic schizophrenia.

In terms of blood-based markers, I found that iron was low relative to psychiatric controls (aOR 0.65, 95% CI 0.44 to 0.97) and this result remained after adjusting for demographic variables. Since conducting this work, another study found that among 44 patients with catatonia, 20 had serum iron below the reference range. (Zingela et al., 2022) My initial hypothesis was that, as iron is a negative acute phase marker, this represented a peripheral inflammatory response, (Rogers et al., 2019) but the lack of difference in C-reactive protein, total white cell count and erythrocyte sedimentation rate does not support this. Another possibility is that low iron is a hallmark of malnutrition, which is likely to occur in catatonia (Clinebell et al., 2014) and could be a consequence of the prolonged hospitalisation. However, there was no evidence for several other markers of malnutrition - low albumin, vitamin B12, folate or creatinine (Keller, 2019; Thongprayoon et al., 2016) – compared to the comparison group. The relationship between iron and catatonia is therefore not clear and may relate to phenotypic heterogeneity, medication use or a more subtle immune response. It is possible that low iron generates hypokinetic symptoms by causing reduced dopaminergic transmission in the basal ganglia, as several enzymes necessary for dopamine synthesis are iron-dependent; (Zucca et al., 2017) this could also explain the close association between catatonia and neuroleptic malignant syndrome. (Rasmussen et al., 2016) Low serum iron has also been demonstrated in a meta-analysis of Parkinson's disease, alongside raised iron in the substantia nigra, demonstrating that alterations in serum and CNS biometals in movement disorders are not necessarily in the same direction. (Genoud et al., 2019) My finding that there was no significant difference between serum iron levels during and between catatonic episodes might suggest an underlying diathesis, but it is also possible that these results were contaminated by other unrecognised episodes of catatonia.

Examining the white cell differential (Table 14) suggests that the total figure masks a more complex picture. Absolute counts of neutrophils are raised (on the adjusted analysis), while lymphocytes, eosinophils and basophils are reduced. Ratios of these cell counts have more recently been used as markers of disease activity in conditions as diverse as chronic obstructive pulmonary disease, solid organ tumours, stroke and acute coronary syndromes, and their use has also been suggested for psychiatric disorders. (Zulfic et al., 2020) There is evidence that the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and monocyte-lymphocyte ratio (MLR) are higher in the manic or hypomanic phase of bipolar affective disorder than in the depressed phase, (Fusar-Poli et al., 2021) while these same ratios have also been found to be higher in relapse of schizophrenia than in

remission. (Özdin and Böke, 2019) In catatonia, one study has found raised NLR compared to healthy controls, although there was no evidence for difference in terms of PLR and MLR. (Sahin et al., 2020) In the present study, I found NLR, MLR and PLR to be raised in catatonia relative to a psychiatric comparison group. It is possible that a relatively low lymphocyte count represents the impact of malnutrition or certain psychotropic medications, (Gergely, 1999; Keller, 2019) but lymphopenia has also been linked to autoimmunity. (Schulze-Koops, 2004) The effect sizes are small, but the prospect that white cell count ratios may reflect disease activity in psychiatric disorders merits further study.

The most striking laboratory finding was the creatine kinase (CK), where the mean result in patients with catatonia (2545 IU/L) was several times higher than that of the comparison group (459 IU/L). Three studies have previously investigated this with only one finding a significant difference, but these all used smaller samples than the present investigation. (Haouzir et al., 2009; Meltzer, 1968; Northoff et al., 1996) One study published since my findings found that 24 out of 44 patients with catatonia had a raised CK, but there was no comparison group. (Zingela et al., 2022) Raised CK may be due to muscle injury resulting from the immobility, posturing and rigidity that occur in catatonia, although the use of intramuscular injections may also have contributed. It is also possible that the group with catatonia was contaminated with patients who may have been developing neuroleptic malignant syndrome, although the result remained significant following exclusion of extreme values. Regardless of mechanism, the presence of high CK may serve as a useful biomarker for catatonia. Raised thyroxine in catatonia (Table 14) is interesting given previous work on periodic catatonia suggesting an increased metabolic rate during episodes and a reduced rate in the intervals, which appeared to be responsive to treatment with thyroid hormones, (Gjessing, 1964, 1975; Gunne and Gemzell, 1956) although I should note that the difference in thyroxine levels in my study was very small.

Given that – as I showed in Chapter 3 – more than 400 cases of catatonia have been reported co-occurring with NMDAR encephalitis and that catatonic features occur in up to 88% of cases of NMDAR encephalitis, (Dalmau et al., 2008; Rogers et al., 2019) I hypothesised that NMDAR antibodies would be present at higher rates in the patients with catatonia. Although my data supported this hypothesis with a large odds ratio (5.6 [95% CI 1.3 to 24.1]), the sample size for antibody tests was small and relied on only three positive results in the group with catatonia. It is consistent with the existing literature, where more severe catatonic features have been found in patients at ultra-high risk of psychosis who have NMDAR antibodies and a continuous measure of NMDAR immunofluorescence found higher positivity in patients with catatonia. (Lin et al., 2017; Pollak, Iyegbe, et al., 2018) However, it requires replication in a prospective sample of patients with and without catatonia that is not subject to selection bias in requesting antibody testing. Further subtyping of immunoglobulins would also be helpful in elucidating the exact immune response.

One particularly striking finding was that patients with catatonia remained in hospital for 134 days longer than other psychiatric inpatients, which represents an enormous degree of morbidity and a substantial economic cost. However, there was no evidence that patients with catatonia had increased mortality in multivariable analysis, in contrast with a recent Japanese study of patients with schizophrenia that found a higher mortality among those with catatonic stupor (OR 4.8 [95% CI 2.0 to 10.6]). (Funayama et al., 2018) The discrepancy might be explained by the restriction of the analysis in Funayama et al.'s study to patients with schizophrenia who had been hospitalised. It is possible that the mortality in my study is not elevated precisely because the patients with catatonia are more unwell than the comparison group and are treated for longer in hospital, where their physical healthcare may be superior to the community. Moreover, some patients may have died before catatonia was formally recorded.

4.5.1 Strengths and limitations

This study had several strengths, notably its large sample size, naturalistic data, psychiatric control group, rigorous standards for defining catatonia and linkage to national records to define mortality. However, there were several limitations, which I consider in terms of the three elements of the study.

Firstly, in terms of the estimate of incidence there is a small possibility that the increase in incidence I observed over the study period is the effect of chance. Using routine clinical records also introduces a selection bias because it relies on clinician identification of disorders and symptoms, which has been found to underestimate catatonia diagnoses. (van der Heijden et al., 2005) It may also preferentially exclude patients without classical features of catatonia, such as those with excited or less acute presentations. The BFCRS has previously been used in paediatric populations, (Grover et al., 2017) but it has not been specifically validated in this group, (Benarous et al., 2016) so it is possible that this also biases the estimates (in either direction) for children. The population used for this study also raises issues of generalisability because South-East London has a particularly high proportion of individuals from an ethnic minority and, possibly relatedly, a high incidence of psychotic disorders compared to other centres in Europe. (Jongsma et al., 2018) Given that more than half of patients in this study had a primary psychotic disorder, it is likely that my estimate of catatonia incidence is higher than the corresponding figure in other locations worldwide.

Secondly, in the case-control study examining blood markers, given that several hypotheses were tested, it is also possible that some findings were due to chance. The fact that only a minority of patients had a valid laboratory result for any given test means that selection bias is possible and exploration of the missing data did suggest small but statistically significant associations with ethnicity and membership of the catatonia group. It is not clear in which direction this might have altered the

findings. Regarding detection of markers of autoimmunity, I was limited to serum samples, but there is evidence that titres are higher in cerebrospinal fluid, thus potentially conferring greater sensitivity, (Dalmau et al., 2008) but this is unlikely to have differentially affected cases and controls. There was evidence of confounding by age, sex and ethnicity, but after adjusting for these factors, the major findings remained. One important unmeasured confounder in the laboratory test results is medication use, which means it is not possible to establish if differences in laboratory test results are due to intramuscular injection or the development of neuroleptic malignant syndrome.

Thirdly, in the cohort study examining hospital admission duration and mortality, despite the large sample size, due to the relatively low number of deaths in the catatonia group, my statistical power for detecting a difference in mortality between the two groups was limited. In terms of missing data, the linkage to national mortality records reduces the potential for bias in the mortality data. It is likely, however, that some apparent discharge dates were actually dates of transfer to other mental health facilities. This is not likely to have differentially affected the cases and controls. Although I adjusted for age, sex, ethnicity and diagnostic group, there are likely to be several other important confounders, including disease severity, smoking status and physical comorbidities. It is not clear how these potential confounders would differ between the cases and controls, so it is hard to estimate their impact. In terms of generalisability, it is possible that the high incidence of psychotic disorders in South-East London makes these findings less applicable to other settings, as catatonia may be less a feature of schizophrenia in other locations and psychotic disorders are known to be associated with increased mortality. (Brown, 1997)

4.6 Conclusions

This study found that the incidence of catatonia is approximately 1 episode per 10,000 person-years. Among psychiatric inpatients, those with catatonia were younger and more likely to be from an ethnic minority. Mortality is similar in catatonia to other psychiatric patients, but duration of psychiatric hospital admission tends to be longer. I replicated a previous finding of low serum iron in catatonia relative to other psychiatric patients, but I did not find that patients with catatonia had evidence of a raised CRP or white cell count. The main weaknesses of this study are the inconsistencies of routinely collected clinical data and a rather atypical catchment area, limiting the generalisability.

5 Clinical neuroimaging findings in catatonia in a case-control study: neuroradiological reports of MRI scans compared to psychiatric inpatients without catatonia

5.1 Summary

5.1.1 Background

Previous neuroimaging studies of catatonia have used small samples with inconsistent results. I aimed to describe the structural neuroradiological abnormalities in clinical MRI brain scans of patients with catatonia and compare them to psychiatric inpatients without catatonia, addressing Aim 3 of this thesis. I report the largest study of catatonia neuroimaging to date.

5.1.2 Methods

In this retrospective case-control study, neuroradiological reports of psychiatric inpatients who had undergone MRI brain scans for clinical reasons were examined. Abnormalities were classified by lateralisation, localisation and pathology. The primary analysis was prediction of catatonia by the presence of an abnormal MRI scan, adjusted for age, sex, ethnicity and psychiatric diagnosis.

5.1.3 Results

Scan reports from 79 patients with catatonia and 711 other psychiatric inpatients were obtained. Mean age (SD) in the cases was 36.4 years (17.3) and 44.5 (19.9) in the control group. Radiological abnormalities were reported in 27 out of 79 cases (34.2%) and in 338 out of 711 in the control group (47.5%), OR 0.57 (0.35 to 0.93), aOR 1.11 (0.58 to 2.14). Among the cases, most abnormal scans had bilateral abnormalities (*n*=23, 29.1%), involved the forebrain (25, 31.6%) and involved atrophy (17, 21.5%).

5.1.4 Conclusions

Patients with catatonia are commonly reported to have brain MRI abnormalities, which largely consist of diffuse cerebral atrophy rather than focal lesions, but there is no evidence that these abnormalities are more common than in other psychiatric inpatients undergoing neuroimaging, after adjustment for demographic variables. Study limitations include a heterogeneous control group and selection bias in requesting scans.

5.2 Background

In Chapter 4, I examined the epidemiology and neuroimmunology of catatonia using electronic healthcare records. Having established a population incidence of catatonia and described the cohort's demographic and clinical features in some detail, I will now proceed in this chapter to examine the structural neuroimaging findings in this group.

As discussed in section 2.7, there is an absence of studies that have compared abnormalities on structural MRI scans that are sufficiently large to be noticed in routine neuroradiological reporting to a control group. The case report literature suggests that structural imaging abnormalities are common, but this is likely susceptible to a reporting bias. It is not clear whether the literature on differences in functional imaging would correspond to abnormalities on structural MRI scans.

This gap in the literature is important because it may be that there is a distinct neuroradiological profile of catatonia. If this exists, it would be of clinical value in supporting a diagnosis of catatonia where such abnormalities exist. Depending on the abnormalities and their implications for further management, it might provide evidence supporting more widespread neuroimaging of patients with catatonia. From a research perspective, finding structural neuroimaging correlates of catatonia might shed light on the elusive pathophysiology of the condition. Perhaps, more likely, it may identify a subgroup of patients with catatonia who have distinct neuroradiological abnormalities: this subgroup could then serve as the basis for further investigation, forming a more neurobiologically homogeneous cohort.

This chapter therefore addresses Aim 3 of this thesis in characterising the structural neuroimaging findings in catatonia. The specific objectives of this chapter are:

3.1 To classify and describe the abnormalities reported in clinical neuroradiological reports of patients with catatonia in a case-control study.

3.2 To compare the frequency of abnormalities reported in clinical neuroradiological reports of psychiatric patients with catatonia to those reported in other psychiatric patients referred for an MRI scan in a case-control study. My hypothesis is that MRI abnormalities will be more commonly reported in patients with catatonia.

5.3 Methods

5.3.1 Study design

A retrospective case-control study was conducted. The population was psychiatric inpatients. The exposure was a diagnosis of catatonia. The control group was psychiatric inpatients without a diagnosis of catatonia. The outcome was the presence of a reported abnormality on a routine clinical structural MRI scan.

The sample size was reached by including all eligible participants.

5.3.2 Setting

The study was conducted using electronic healthcare records from South London and Maudsley NHS Foundation Trust, London, UK, using the CRIS system, as described in section 4.3.1.

5.3.3 Participants

I have described the selection of participants in detail in section 4.3. For inclusion in this study, as previously, participants had to have catatonia diagnosed by a clinician, evidence of at least two catatonic features on the BFCSI and an index date for the catatonia. In addition, for this neuroimaging study, they needed to have a clinical neuroradiological report of a structural MRI scan conducted either prior to the index date or within 90 days after the index date. MRI scans were available from 2008 to 2018, inclusive. The 90-day window was used as a pragmatic cut-off point, as after this date there is a higher probability that abnormalities may have arisen after a catatonic episode. Where there were multiple scans available for one patient, the scan that was nearest to the index date was used. This approach was used because there were very few instances of additional scans for any particular patient, so a multilevel model with scan and patient as separate levels would have added very little value at the expense of added model complexity. This procedure is illustrated in Figure 8.

For the control group, participants needed to be psychiatric inpatients with no history of catatonia who had had a structural MRI scan conducted. The control group had a range of underlying diagnoses, just as the catatonia cases did. All patients with catatonia in the final analysis had also been psychiatric inpatients.

5.3.4 Variables

The derivation, definition and role of variables in the analysis are shown in Table 19. Routine clinical structural MRI scans were reported by consultant neuroradiologists, of whom there were eight. The exposure of interest was an abnormal MRI scan, as judged by the reporting neuroradiologist. The clinical scanner was a 1.5 Tesla GE HDx, with scans collected for clinical reporting including high-resolution T1-weighted, T2-weighted and FLAIR sequences without contrast. The reports of MRI scans

were compiled into a spreadsheet. Two investigators (Roshell Jeyaventhan and Ramya Thanikasalam) categorised the scans as normal or abnormal based on the reports under my supervision. Only intracranial abnormalities were considered relevant. They then used a proforma I had designed to categorise reported abnormalities by their anatomical location, pathological description and lateralisation. The two investigators were blinded to each other's assessments and to the diagnostic group. Where there was disagreement between the two investigators, I arbitrated.

The process of categorising abnormalities produced a number of small cells, due to several rare abnormalities. I therefore grouped anatomical areas by embryological brain structure and grouped pathologies by main underlying mechanism. This process was conducted blind to group membership.

Table 19: Derivation, definition and role of variables in the analysis

Variable	**Derivation**	**Definition**	**Role in analysis**			
			Outcome	Exposure	Covariate	Used in imputation model
Diagnosis of catatonia	Free text	Catatonia identified by a clinician and at least 2 signs from the BFCSI present.	●			●
Validity of MRI scan report	Linkage to neuroradiological reports on structural MRI scans	Scan considered valid if an adequate scan took place and was reported				●
Abnormality on MRI scan report	Linkage to neuroradiological reports on structural MRI scans	Reports by a consultant neuroradiologist. See text for process of coding scans.		●		●
Index date	Catatonia cases: date of first identified catatonic episode. Control group: date of hospital admission.	Catatonia cases: free text. Control group: structured field.				●
Date of birth	Structured field	As entered by hospital administration. Recorded to nearest month to preserve anonymity.				●

Death within follow-up period	Linkage to Office for National Statistics mortality data	Binary variable indicating whether death had occurred within follow-up period				●
Date of death	Linkage to Office for National Statistics mortality data	-				●
Date of scan	Structured field	Date that MRI was performed				●
Age at index date	Structured field	Time from birth to index date				●
Age at scan date	Structured field	Time from birth to date of scan			●	●
Sex	Structured field	As entered by hospital administration: male/female			●	●
Ethnicity	Structured field	As entered by hospital administration. Categories were grouped according to the preferred categories of the UK Office for National Statistics. (Office for National Statistics, 2011) Other ethnic group was combined with Mixed / Multiple ethnic groups to avoid small cell sizes. For the regression model, to increase statistical power Black ethnicity was compared to all other ethnic groups.			●	●
Involuntary detention	Structured field	Detained under the Mental Health Act within 2 weeks following the index date				●
Diagnosis	Structured field	Primary ICD-10 diagnosis grouped as organic and neurodevelopmental disorders (ICD-10 codes F00-F09, F70-89, F90, F95 and non-F codes); schizophrenia and related disorders (F20-F29); mood disorders (F30-F39); neurotic disorders (F40-59); personality and behavioural disorders (F50-69, F91-F94, F98),			●	●

		and substance use disorders (F10-F19). Where multiple primary diagnoses had been given, the most recent diagnosis prior to the index date was used. If no diagnosis had been given prior to the index date, the earliest diagnosis up to six months after the index date was used.				
ECT use	Structured field	ECT administered within 2 weeks after index date				⚫
Diastolic blood pressure	Natural language processing of free text	Nearest recording within 2 weeks of index date				⚫
Systolic blood pressure	Natural language processing of free text	Nearest recording within 2 weeks of index date				⚫
Referral – index date lag	Structured field and free text	Time from first referral to South London and Maudsley NHS Foundation Trust to index date				⚫
Index date – documentation lag	Free text	Time from index date to documentation of episode				⚫
Catatonia end date	Free text	Date that catatonia was recorded no longer to be present				⚫
Health of the Nation Outcome Scale (HoNOS) score	Structured field	Score nearest prior to and including index date				⚫
Health of the Nation Outcome Scale (HoNOS) date	Structured field	Date of score nearest prior to and including index date				⚫
Admission duration	Structured field	For inpatient episodes, time from hospital admission in which episode occurred to hospital discharge				⚫

MMSE score	Natural language processing of free text	Nearest recording within 2 weeks of index date				●
Number of episodes	Free text	For catatonia cases: number of catatonia episodes				●

5.3.5 Statistical analysis

I investigated whether having an abnormal MRI scan was associated with greater odds of reporting catatonia, using univariable and multivariable logistic regression models adjusted for age, sex, ethnicity and diagnostic group.

Given the differing proportions of organic or neurodevelopmental diagnoses across the groups, I conducted a sensitivity analysis where I excluded these diagnoses. As a secondary analysis, among the abnormal scans, I conducted a logistic regression for catatonia based on the number of abnormalities per scan, adjusted for age, sex, ethnicity and diagnostic group.

I analysed lateralisation, anatomical location, and pathology by the number of scans that had at least one abnormality in the specified category. This was done to avoid scans with many abnormalities excessively weighting the analyses. To calculate the differences between proportions having different categories of abnormalities, I used Fisher's exact test, as there were numerous small cell sizes.

I adjusted for age on date of scan, sex, ethnicity and diagnostic group, as they have all previously been associated with the exposure (brain MRI abnormalities) (Choi et al., 2020; Debette et al., 2019; Gunning-Dixon et al., 2009; Liu et al., 2015; Nasrallah et al., 1990) and the outcome (catatonia). (Dutt et al., 2011; Hutchinson et al., 1999; Smith et al., 2012; Stöber et al., 1998) Given the temporal primacy of age, sex and ethnicity, they cannot be on the causal pathway. Diagnostic group might be on the causal pathway from MRI abnormalities to development of catatonia, but I designed the study to investigate whether there is any relationship between MRI abnormalities and catatonia, beyond merely an alteration in the underlying disorders.

In terms of missing data, the main missing variable for the analysis was the exposure, i.e. a result from an MRI scan. Further description of the missing data are provided in section 5.4.2. Given that there were marked differences between the patients who did and did not have a scan, it is not possible to support a missing completely at random (MCAR) hypothesis. The remaining hypotheses are that the data are missing at random (MAR) or missing not at random (MNAR). Given that these are clinical MRI scans and only a minority of patients had a scan requested, it is likely that there were factors related to the clinical presentation that were associated with the decision to request a scan. These factors

may be at least partly present in the available data (e.g. age, diagnosis, disease severity [as indicated by the HoNOS score]). It is difficult to know whether such available data completely explain the missingness, so it is impossible to know whether the data are still missing not at random. However, the missing at random hypothesis is more plausible when a multiple imputation model with more variables is used and this is likely to reduce a bias introduced by missing data. (Pedersen et al., 2017). The working assumption was therefore made that the data were missing at random.

As a sensitivity analysis, I therefore imputed missing exposure data for participants with complete outcome data using multiple imputation by chained equations. I imputed using all variables included in the models as well as a number of auxiliary variables that were either associated with one of the variables of interest or with missingness of one of the variables of interest. The variables included in the final imputation model are indicated in Table 19. These variables were chosen based on the data available from the CRIS extraction and an inclusive approach was adopted, as there is evidence that this can reduce the bias subsequent estimates. (Azur et al., 2011) The number of imputations was determined through an iterative approach, starting with 5 imputed datasets and increasing the number of imputations in increments of 5 until results converged. The final number of imputations performed was 20.

The analysis used Stata MP version 15.1. This chapter is written according to the STROBE guidelines (von Elm et al., 2007) and the STROBE checklist can be found in Table 20. Statistical significance was set to 0.05.

Table 20: STROBE Checklist

	Item No	**Recommendation**	**Location**
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5.1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2.7 5.2
Objectives	3	State specific objectives, including any prespecified hypotheses	5.2
Methods			
Study design	4	Present key elements of study design early in the paper	5.3.1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5.3.2

Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	5.3.3
		(*b*) For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5.3.4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5.3.4
Bias	9	Describe any efforts to address potential sources of bias	5.3.5
Study size	10	Explain how the study size was arrived at	5.3.1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5.3.4 5.3.5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5.3.5
		(*b*) Describe any methods used to examine subgroups and interactions	5.3.5
		(*c*) Explain how missing data were addressed	5.3.5 5.4.2
		(*d*) If applicable, explain how matching of cases and controls was addressed	N/A
		(*e*) Describe any sensitivity analyses	5.3.5
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 8
		(b) Give reasons for non-participation at each stage	Figure 8
		(c) Consider use of a flow diagram	Figure 8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 23
		(b) Indicate number of participants with missing data for each variable of interest	Table 23

Outcome data		15*	Report numbers in each exposure category, or summary measures of exposure	Table 24
Main results		16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5.4.4
			(*b*) Report category boundaries when continuous variables were categorized	N/A
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		5.4.5 5.4.6 5.4.7
Discussion				
Key results	18	Summarise key results with reference to study objectives		5.5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		5.5
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		5.5
Generalisability	21	Discuss the generalisability (external validity) of the study results		5.5
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		5.3.6

5.3.6 Funding

The study was supported by the NIHR and the Wellcome Trust. The funders played no part in the design or conduct of the study, or in the decision to publish.

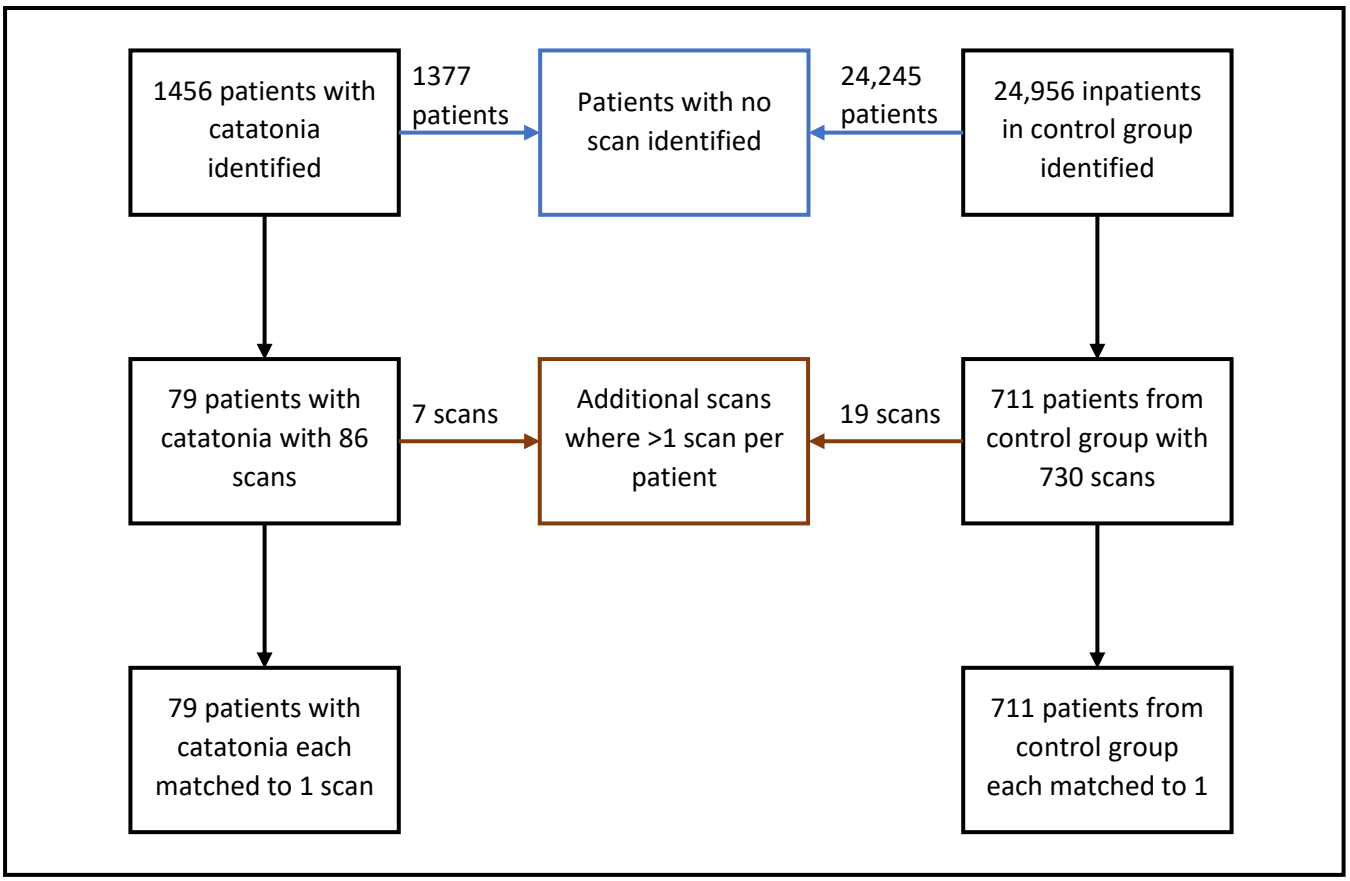
5.4 Results

5.4.1 Participants

Out of 1,456 patients with catatonia and 24,956 patients in the control group, complete MRI scan reports were extracted for 790 subjects who had a total of 816 scans. After extracting one scan per patient, there were 79 scans in the catatonia group (5.4% of all patients with catatonia) and 711 scans

in the control group (2.8% of all patients in the control group), as illustrated in Figure 8. 188 included scans were conducted prior to the index date and 602 were conducted on or after the index date. The median time from index date to scan was 27 days (IQR 5 to 48) and the range was -2679 to 90 days. 69 scans were conducted within 2 weeks of the index date.

Figure 8: Flowchart of patient selection



5.4.2 Missing data

Scan result was missing for 25,622 (97.0%) participants, age at index for 1,904 (7.2%), sex for 4 (0.0%) and ethnicity for 393 (1.5%). A control of patients with observed and missing MRI scans is shown in Table 21. Patients of Black ethnicity appeared more likely to have an MRI scan, but the groups were similar in terms of age and sex.

Table 21: Comparison of patients with observed and missing valid MRI scan reports

Variable	**Patients with a valid MRI scan (*N*=790)**	**Patients without a valid MRI scan (*N*=25,622)**
Age at index, mean (SD)	43.9 (19.8)	40.2 (17.0)

Sex, *n* (%)		
- Male	439 (3.1)	13,859 (96.9)
- Female	351 (2.9)	11,759 (97.1)
- Not stated	0 (0.0)	4 (0.0)
Ethnicity, *n* (%)		
- White	410 (2.6)	15,427 (97.4)
- Black	275 (4.0)	6,541 (96.0)
- Asian	49 (3.5)	1,335 (96.5)
- Mixed / Other	48 (2.4)	1,934 (97.6)
- Not stated	8 (2.0)	385 (98.0)

The observed and imputed data are compared in Table 22.

Table 22: Comparison of properties of observed and imputed data

Variable	**Observed data**		**Imputed data (across 20 datasets)**	
	Total number of values, N	*n (%)*	*Total number of values, N*	*n (%)*
Sex, male	26,408	14,298 (54.1)	80	47 (58.8)
Ethnicity, Black	26,019	6,816 (26.2)	7860	1866 (23.7)
Valid MRI scan report, abnormal	790	365 (46.2)	512,440	226,128 (44.1)
	Total number of values, N	*Mean (SD)*	*Total number of values, N*	*Mean (SD)*
Age at scan, years	1904	43.5 (19.4)	490,160	41.4 (17.1)

5.4.3 Demographic and disease-related characteristics

Table 23 summarises the demographic and disease-related data of the participants in this study. Mean age at the time of the scan was 36.4 years (SD 17.3, range 10 to 78) for the catatonia group and 44.5 years (SD 19.9, range 7 to 93) for the control group. Handedness of subjects is not available in this dataset.

Table 23: Demographic and disease-related characteristics of catatonia and control groups.

	Catatonia group (*N* = 79)	**Control group (*N* = 711)**

	n	%	*n*	%
Sex				
- **Female**	35	44.3	316	44.4
- **Male**	44	55.7	395	55.6
Ethnicity				
- **White**	21	26.6	389	54.7
- **Asian / Asian British**	4	5.1	45	6.3
- **Black / African / Caribbean / Black British**	49	62.0	226	31.8
- **Mixed / Multiple ethnic groups**	1	1.3	12	1.7
- **Other ethnic group**	3	3.8	32	4.5
- **Not stated**	1	1.3	7	1.0
Primary diagnosis				
- **Organic or neurodevelopmental disorder**	3	3.8	124	17.4
- **Schizophrenia and related disorders**	50	63.3	266	37.4
- **Mood disorders**	12	20.1	143	20.1
- **Neurotic disorders**	3	3.8	31	4.4
- **Personality and behavioural disorders**	5	6,3	31	4.4
- **Substance use disorder**	2	2.5	45	6.3
- **Not stated**	4	5.1	69	9.7
Involuntary detention	55	69.6	459	64.6

5.4.4 Abnormalities

In total, 365 out of 790 scans (46.2%) were reported as abnormal. As shown in Table 24, 34.2% of the catatonia group had an abnormal scan, compared to 47.5% of the control group. In the unadjusted complete-case analysis, having an abnormal MRI scan was associated with lower odds of a diagnosis of catatonia with an odds ratio (OR) of 0.57 (95% CI 0.35 to 0.93), *p*=0.03. After adjustment for confounders (age, sex, ethnicity and diagnostic group), there was no longer evidence of an association (OR 1.11 (0.58 to 2.14), *p*=0.75). In sensitivity analyses run on imputed datasets, the results were consistent with those of complete case analyses with an OR of 0.92 (95% CI 0.48 to 1.74) and an adjusted OR of 1.30 (95% CI 0.53 to 3.20). Abnormalities by diagnostic group are reported in Table 25.

Table 24: Numbers of normal and abnormal scans in catatonia and control groups

	Scan normal		**Scan abnormal**		**Total**
	n	%	*n*	%	
Catatonia group, *n* (%)	52	65.8	27	34.2	79
Control group, *n* (%)	373	52.5	338	47.5	711
Total, *n* (%)	425	53.8	365	46.2	790

Table 25: MRI scan abnormalities by diagnostic group

Primary diagnosis	**Catatonia group**		**Control group**	
	Total *n*	Abnormal *n* (%)	Total *n*	Abnormal *n* (%)
Organic or neurodevelopmental disorder	3	3 (100)	124	102 (82)
Schizophrenia and related disorders	50	14 (28)	266	92 (35)
Mood disorders	12	6 (50)	143	71 (50)
Neurotic disorders	3	1 (33)	31	14 (45)
Personality and behavioural disorders	5	2 (40)	31	8 (24)
Substance use disorder	2	0 (0)	45	27 (60)
Not stated	4	1 (25)	69	24 (35)

Among the scans reported as abnormal, there were between 1 and 10 abnormalities. In the patients with catatonia, the median number of abnormalities was 2 (IQR 1 to 3). In the control group, the median number of abnormalities was 2 (IQR 1 to 4). The unadjusted OR for catatonia diagnosis as predicted by the number of abnormalities was 0.84 (95% CI 0.65 to 1.08), p=0.17. After adjustment for age, sex, ethnicity and diagnostic group, the OR was 0.96 (95% CI 0.75 to 1.23), p=0.74.

5.4.5 Lateralisation

Table 26 shows that most abnormal scans had at least one bilateral abnormality in both the catatonia and control groups. There was no evidence of difference in lateralisation of abnormalities between the groups (p = 0.98).

*Table 26: Abnormalities by lateralisation, localisation and pathology: number of scans in each group that had at least one abnormality with the specified properties **

	Catatonia group (*N*=79)		**Control group (*N*=711)**	
	n	%	*n*	%
Lateralisation				
- **Midline**	3	3.8	43	6.1

- **Bilateral**	23	29.1	300	42.2
- **Right**	6	7.6	67	9.4
- **Left**	5	6.3	74	10.4
Anatomical location				
- **Midbrain**	0	0	7	1.0
- **Forebrain**	25	31.6	312	43.9
- **Hindbrain**	9	11.4	82	11.5
- **White matter tract**	1	1.3	25	3.5
- **Non-brain**	1	1.3	8	1.1
Pathology				
- **Atrophy**	17	21.5	210	29.5
- **Small vessel disease**	9	11.4	139	19.6
- **White matter lesion**	8	10.1	74	10.4
- **Stroke**	2	2.5	58	8.2
- **Unspecified focal lesion**	2	2.5	17	2.4
- **Gliosis and encephalomalacia**	1	1.3	47	3.6
- **Prominent perivascular spaces**	1	1.3	11	1.6
- **Vascular abnormality**	1	1.3	6	0.8
- **Ectopia**	1	1.3	4	0.6
- **Hypoplasia**	1	1.3	1	0.1
- **Contusion**	1	1.3	18	2.5
- **Cyst**	0	0	10	1.4
- **Demyelination**	0	0	6	0.8
- **Cavum**	0	0	5	0.7
- **Wallerian degeneration**	0	0	4	0.6
- **Tumour**	0	0	2	0.3
- **Midline shift**	0	0	2	0.3
- **Enlargement**	0	0	2	0.3
- **Malformation of cortical development**	0	0	2	0.2
- **Extra axial haemorrhage**	0	0	1	0.1
- **Sclerosis**	0	0	1	0.1
- **Ulegyria**	0	0	1	0.1
- **Progressive multifocal leukoencephalopathy**	0	0	1	0.1
- **Absence**	0	0	1	0.1

*Each scan may appear in more than one category, e.g. a scan may have a midline and a right-sided abnormality

5.4.6 Anatomical Location

Abnormalities were reported across various brain regions, as shown in Table 26. The majority of abnormalities were in the forebrain in both groups. I found no evidence for differences in anatomical location of abnormalities between the groups (p = 0.73). In the catatonia group, among 25 scans with forebrain abnormalities, the specific location of the abnormalities was diffuse cerebral (n=18), frontal (n=7), parietal (n=4), temporal (n=3), occipital (n=1), basal ganglia (n=1), thalamus (n=1), pituitary gland (n=1) and optic nerve (n=1). (Some scans had more than one abnormality.) In terms of the 9 scans with hindbrain abnormalities, the specific locations were the cerebellum (n=6) and pons (n=3).

5.4.7 Pathology

The numbers of scans reporting different categories of pathology are reported in Table 26. The most common pathologies in both groups were brain atrophy and small vessel disease. Additionally, the scans of the catatonia group showed similar frequencies of white matter lesions and small vessel disease. There was no evidence for a difference in pathology of abnormalities between the groups (p = 0.75).

5.5 Discussion

Neuroimaging abnormalities in patients with catatonia have previously been described in case reports and other studies with small sample sizes, often without a control group. This study used a large dataset to describe common structural neuroimaging findings in patients with catatonia and compared these to psychiatric patients without catatonia.

In terms of descriptive data, I found that MRI abnormalities are commonly reported in individuals with catatonia who have a scan, being present in 27 out of 79 scans (34%). It was common for there to be more than one abnormality in each scan. The majority of abnormal scans had at least one abnormality reported that was bilateral (23 out of 27), that affected the forebrain (25 out of 27, of which 18 had a diffuse cerebral distribution) and that involved atrophy (17 out of 27), although some of these scans also had other types of abnormalities reported. However, when I compared the scans between the groups with and without catatonia, I found no differences in the proportion of scans reported to have an abnormality after adjustment for age, sex, ethnicity and diagnostic group. Secondary analyses also found no evidence for a difference in the number of abnormalities, lateralisation, anatomical location or pathology.

To my knowledge, this is the largest study of catatonia neuroimaging published to date. (Haroche et al., 2020) It also has the advantage of representing patients with catatonia across a range of underlying disorders and it has an appropriate control group of psychiatric inpatients without catatonia.

However, there are a number of evident limitations, many inherent to the use of electronic healthcare records. The most important bias relates to the fact that the patients with neuroimaging are likely to be unrepresentative of all psychiatric inpatients due to the various reasons that they may be referred for a scan. The reasons for ordering a scan were not available and are likely to differ between the catatonia and control groups, so this would potentially lead to a selection bias. The characteristics of the control group have been shown to have a substantial effect on outcomes in studies of neuroimaging in psychiatric patients. (Chua and McKenna, 1995) Where a patient did not have an MRI scan, this was generally because it was not requested by the clinician. There is no consensus on whether many groups of psychiatric patients should undergo neuroimaging, but there is evidence that patients who are older and who are suspected to have neurological diagnoses are more likely to be referred for neuroimaging. (Mueller et al., 2006; Rego and Velakoulis, 2019)

In terms of missing data, on occasion, an MRI scan may have been performed in another hospital, it may have been performed outside of the window for this study or the patient's lack of cooperation meant that no useful data could be extracted from the scan. Sex and ethnicity were occasionally missing (in 0.02% and 1.5% respectively) in the overall dataset and this was due to an absence of administrative coding of this information in the patient records. Although my sensitivity analysis using multiple imputation is likely to provide a less biased estimate than complete case analysis, the model was not able to include all the variables that would ideally be present to assert a missing at random hypothesis (such as the presence of focal neurological signs, pre-existing neurological disorders, seizures or head injury), (Rego and Velakoulis, 2019) so it is likely that it is not a wholly adequate method of dealing with the missing data.

In terms of confounding, I was able to adjust my analysis for demographic variables, but there are likely to be other relevant variables (such as cardiovascular risk factors or cognitive function) for which data were not available. Neuroradiologists sometimes reported findings differently and likely had different thresholds for what was worthy of mention. These reports may have been biased by the clinical information presented and the questions asked when the scan was requested. This may in part explain why the proportion of individuals with catatonia with an abnormal MRI scan is somewhat lower than some previous smaller studies. Medda et al. (2015) described 26 patients with catatonia resistant to benzodiazepines, finding that the CT or MRI scan was abnormal in 17 (65%, 95% CI 44 – 83%). Smith et al. (Smith et al., 2012) examined the MRI scans of 31 patients with catatonia, finding abnormalities in at least 18 (58%, 95% CI 39 – 75%). It is possible that my study provides a more conservative estimate because its larger size means it is less susceptible to reporting bias.

There is, however, some consistency with other structural neuroimaging studies in terms of the type of abnormalities. Three other studies have shown extensive or generalised atrophy (or its proxy, enlarged CSF spaces) as the most common neuroimaging abnormality. (Joseph et al., 1985; Medda et al., 2015; Smith et al., 2012) A large number of case reports of focal lesions associated with catatonia have been reported, but most of these are cases of diffuse or multiple abnormalities. (Haroche et al., 2020) Taken together, my findings support a weight of evidence that catatonia is associated with dysfunction of brain networks, rather than being the product of damage to isolated brain regions. (Fricchione and Beach, 2019) This is consistent with a quantitative study of MRI images that found reduced grey matter volumes in individuals with catatonia in areas within the frontothalamic and corticostriatal networks. (Hirjak, Rashidi, et al., 2020)

However, when I examined the comparison to psychiatric patients without catatonia, there is no evidence for a difference in the proportion of abnormal scan reports after adjustment for demographic variables. To my knowledge, no prior studies had compared clinical neuroradiological reports of MRI scans in patients with catatonia to a psychiatric comparison group. Two studies conducted this analysis using CT scan results, but one had just 5 patients with catatonia, (Joseph et al., 1985) while the other focussed solely on cerebellar atrophy. (Wilcox, 1991) Since the current study was published, a similarly designed study in France (in which I had a small part) compared the structural MRI reports of 60 patients with catatonia to 60 patients referred with headache. (Magnat et al., 2022) As in my study, the frequency of abnormalities between the groups was similar and abnormalities were white matter abnormalities and generalised atrophy. This emphasises the high prevalence of non-specific brain abnormalities in patients with psychiatric disorders, especially schizophrenia and other neuropsychiatric conditions severe enough to require admission, and the need for a relevant comparison group in studies of catatonia. Previous work with data from the Maudsley Hospital found that only 12.3% of MRI scans were abnormal, but in this sample the mean age was 26 (compared to 44.5 for my control group) and all were under evaluation for first-episode psychosis. (Falkenberg et al., 2017) It seems likely that the older age and greater disease severity of my control group led to the detection of more abnormalities, but it is notable that, even after adjusting for age, there was no evidence that individuals with catatonia were more likely to have an abnormal MRI scan. Adjustment or matching for factors such as psychopathology or neurological signs might be helpful.

In conclusion, patients with catatonia commonly have MRI scan abnormalities reported, most frequently diffuse atrophy, but there was no evidence that such abnormalities occur at a higher frequency than in other psychiatric inpatients. This study does not support the use of MRI scans to support the diagnosis of catatonia. This is consistent with there being a basic neurobiological

vulnerability to the condition, which relapses and remits, but which may be specifically driven by metabolic or physiological dysfunction. Researchers should consider the benefits of using large clinical samples to study patients with relatively rare and hard to recruit conditions such as catatonia while mitigating the lack of systematic detail inherent in the qualitative neuroradiological evaluation of clinical MRI scans. However, using routine healthcare records has notable limitations including heterogeneous control groups, selection bias and varying reporting thresholds from radiologists. Quantitative volumetric analysis or functional neuroimaging techniques, such as arterial spin labelling, in operationally defined cases and a comparison group chosen to minimise selection bias remains the ideal research design and longitudinal studies assessing the stability of neuroimaging abnormalities in catatonia will also be important.

6 The role of the electroencephalogram (EEG) in determining the aetiology of catatonia: a systematic review and meta-analysis of diagnostic test accuracy

This chapter has previously been published in an adapted form in EClinicalMedicine*.* (Hosseini et al., 2023)

6.1 Summary

6.1.1 Background

In a systematic review and meta-analysis, I aimed (a) to describe the abnormalities reported in the EEGs of patients with catatonia and (b) to ascertain the performance of the EEG in determining whether catatonia has an underlying general medical condition or primary psychiatric disorder, addressing Aim 4 of this thesis.

6.1.2 Methods

Medline, EMBASE, PsycInfo, and AMED were searched from inception to May 11, 2022 for articles published in peer-reviewed journals that reported EEG findings in catatonia of a medical or psychiatric origin and were reported in English, French, or Italian (PROSPERO CRD42021239027). The reference standard was the final clinical diagnosis. I prespecified two types of studies to overcome the limitations anticipated in the data: larger studies ($n \geq 5$), which were suitable for formal meta-analytic methods but generally lacked detailed information about participants, and smaller studies ($n < 5$), which were unsuitable for formal meta-analytic methods but had detailed individual patient level data, enabling additional sensitivity analyses. Risk of bias and applicability were assessed with the QUADAS-2 tool for larger studies, and with a published tool designed for case reports and series for smaller studies. The primary outcomes were sensitivity and specificity, which were derived using a bivariate mixed-effects regression model.

6.1.3 Results

355 studies were included, spanning 707 patients. Of the 12 larger studies (5 cohort studies and 7 case series), 308 patients were included with a mean age of 48.2 (SD = 8.9) years. 85 (52.8%) were reported as male and 99 had catatonia due to a general medical condition. In the larger studies, I found that an abnormal EEG predicted a medical disorder underlying catatonia with a sensitivity of 0.82 (95% CI 0.67 to 0.91) and a specificity of 0.66 (95% CI 0.45 to 0.82) with an I^2 of 74% (95% CI 42 to 100%). The area under the summary ROC curve indicated excellent discrimination (AUC=0.83). The positive likelihood ratio was 2.4 (95% CI 1.4 to 4.1) and the negative likelihood ratio was 0.28 (95% CI 0.15 to 0.51). Only

5 studies had low concerns in terms of risk of bias and applicability, but a sensitivity analysis limited to these studies was similar to the main analysis.

Among the 343 smaller studies, 399 patients were included, resulting in a sensitivity of 0.76 (95% CI 0.71 to 0.81), specificity of 0.67 (0.57 to 0.76) and AUC=0.71 (95% CI 0.67 to 0.76). In multiple sensitivity analyses, the results were robust to the exclusion of reports of studies and individuals considered at high risk of bias. Features of limbic encephalitis, epileptiform discharges, focal abnormality, or status epilepticus were highly specific to medical catatonia, but features of encephalopathy had only moderate specificity and occurred in 23% of the cases of psychiatric catatonia in smaller studies.

6.1.4 Discussion

In cases of diagnostic uncertainty, the EEG should be considered alongside other investigations to ascertain whether the disorder underlying catatonia is a general medical condition. The main limitation of this review is the differing thresholds for considering an EEG abnormal between studies.

6.1.5 Funding

Wellcome Trust, NIHR Biomedical Research Centre at University College London Hospitals NHS Foundation Trust

6.2 Background

In the previous two chapters, I have used electronic healthcare records to investigate the neuroimmunology, epidemiology and structural neuroimaging of catatonia. In order to examine electroencephalographic findings in catatonia, I am moving away from this dataset, as it lacks systematic electroencephalogram (EEG) reporting. Instead, in the current chapter, I conduct a systematic review to examine the evidence in the existing literature.

In clinical practice, one of the most challenging dilemmas in patients with catatonia is ascertaining whether it is associated with a conventionally defined primary psychiatric disorder, such as major depressive disorder, bipolar affective disorder, schizophrenia or a neurodevelopmental disorder, or whether it is associated with a general medical condition, such as status epilepticus, autoimmune encephalitis, neurodegenerative disease, a space-occupying lesion, or medications. [17] These varying disorders can require dramatically different treatments, so the distinction is critical.

In current practice, a standard work-up for catatonia may include a detailed history and physical examination as well as a wide range of blood tests, cerebrospinal fluid analysis, a urine drug screen, neuroimaging and EEG, but this depends on the clinical scenario. [18–21] Recommendations vary, however, with some authors suggesting that all patients with catatonia have an EEG [18,20,22] and others advising that an EEG is merely considered in catatonia [19,23] or that it is used only in certain circumstances. [21,24] According to recent observational data from a large US study in acute hospitals, only 4.6% of patients with catatonia had an EEG, compared to 6.4% who underwent a lumbar puncture. [25] Overall, the evidence base for use of the EEG remains uncertain and practice appears to differ. There are two clinical scenarios where there is an obvious benefit of EEG recording in catatonia. One is in the context of possible non-convulsive status epilepticus [26] and the other is in suspected NMDA receptor encephalitis, where a highly specific finding of extreme delta brush is sometimes evident. [27]

However, overall there is currently very little evidence on which to base the decision as to whether an EEG is helpful in catatonia. In particular, the sensitivity, specificity, positive predictive value and negative predictive value of the EEG in identifying whether there is a medical or psychiatric cause of catatonia is unclear. Given that most studies of catatonia have small sample sizes,[28] there is a need to synthesise data from multiple reports to reach robust conclusions. A previous systematic review from 1998 examined EEG abnormalities in catatonia due to a medical condition, finding that 84.7% of cases had an abnormality, most commonly diffuse slowing, but this did not include the more recent literature and there was no comparison group of catatonia due to a psychiatric illness. [29] Moreover, the correlation between specific EEG abnormalities and the aetiology of catatonia has not been systematically studied but has the potential to be more useful than a simple normal-abnormal EEG classification.

I conducted a systematic review and meta-analysis of the diagnostic test accuracy of the standard clinical EEG in catatonia for ascertaining whether catatonia is due to a medical cause (as opposed to a psychiatric cause). As a secondary objective, I aimed to characterise the specific EEG abnormalities in catatonia, both medical and psychiatric.

6.3 Methods

6.3.1 Search strategy

In this systematic review and meta-analysis of diagnostic test accuracy, I used Ovid to search Medline® All, EMBASE Classic + EMBASE, APA PsycInfo, and AMED (Allied and Complementary Medicine). These databases represent a range of the medical, psychological and allied health literature. The overall approach to developing a search in each database was to combine synonyms for catatonia with

synonyms for electroencephalography without limits. The search was originally run on 23/02/2021 and updated on 11/05/2022. The full search strategy for all databases is shown in Table 27.

Table 27: Ovid search strategy

Database	Search terms
Medline® All	1. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh, nm, kf, ox, px, rx, ui, sy] 2. exp Catatonia/ or exp Schizophrenia, Catatonic 3. 1 or 2 4. (eeg or electroencephalogr* or electrocerebral or telemetr*).mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh, nm, kf, ox, px, rx, ui, sy] 5. exp Electroencephalography/ 6. 4 or 5 7. 3 and 6 8. 7 use ppezv
EMBASE Classic + EMBASE	9. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh, nm, kf, ox, px, rx, ui, sy] 10. exp catatonia/ or exp catatonic schizophrenia/ 11. 9 or 10 12. (eeg or electroencephalogr* or electrocerebral or telemetr*).mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh, nm, kf, ox, px, rx, ui, sy] 13. exp electroencephalogram/ or exp electroencephalograph/ 14. 12 or 13 15. 11 and 14 16. 15 use emczd
APA PsycInfo	17. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh, nm, kf, ox, px, rx, ui, sy] 18. exp catatonia/ or exp catatonic schizophrenia/ 19. 17 or 18 20. (eeg or electroencephalogr* or electrocerebral or telemetr*).mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh, nm, kf, ox, px, rx, ui, sy]

	21. exp electroencephalography/ 22. 20 or 21 23. 19 and 22 24. 23 use psyh
AMED (Allied and Complementary Medicine)	25. catatoni*.mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh, nm, kf, ox, px, rx, ui, sy] 26. exp catatonia/ 27. 25 or 26 28. (eeg or electroencephalogr* or electrocerebral or telemetr*).mp. [mp=ab, hw, ti, tn, ot, dm, mf, dv, kw, fx, dq, tc, id, tm, mh, nm, kf, ox, px, rx, ui, sy] 29. exp electroencephalography/ 30. 28 or 29 31. 27 and 30 32. 32. 31 use amed
Combined databases	33. 8 or 16 or 24 or 32 34. remove duplicates from 33

In addition to searching databases, reference lists of included articles were examined and other members of the study team contacted significant researchers in the field to identify further works. Duplicate articles were first identified automatically using Ovid, then manually by identifying similar titles and comparing article citations.

6.3.2 Selection criteria

Inclusion criteria were observational or interventional human studies published in a peer-reviewed journal in English, French, or Italian. Clinical trials, cohort studies, case-control studies, cross-sectional studies, case series, and case reports were eligible. Individuals must have had a diagnosis of catatonia in the opinion of the authors of the original study and an aetiology for catatonia must have been described (at a minimum stating whether it was medical or psychiatric). There was no age restriction and individuals could be in any clinical setting. A clinical EEG (either scalp or intracranial) must have been performed while the individual was experiencing catatonia and there must be a clinical report in the article that identified – at a minimum – whether it was considered normal or abnormal. For the larger studies, which underwent a formal meta-analysis, there was an additional inclusion criterion of having at least 5 eligible patients. A cut-off of 5 was chosen as a pragmatic compromise between

reducing selection bias and the requirements of formal meta-analytic methods on the one hand, and the small sample sizes in most studies of EEG diagnostic test accuracy on the other, (Bachmann et al., 2006; Takwoingi et al., 2015) which I anticipated would be particularly the case for a rare disorder.

Conference abstracts were excluded because they generally lack detailed information about case histories. For the included articles, I assumed, for example, that – where only certain medications were mentioned – other medications were not used. Given the concision necessary for a conference abstract, this assumption may not hold. Articles in which it was not clear that individual patients had catatonia were excluded. Articles in which only quantitative EEG (with, for example, spectral analysis) or an EEG described only in terms of the absence of certain abnormalities (and thereby not commenting on whether other abnormalities were present) were also excluded. I also excluded articles where the only report of an EEG was during electroconvulsive therapy or during pharmacological seizure induction, as these cases would not provide a representative reflection of cortical electrographic activity.

Two investigators (Paris Hosseini and Karrish Devan) assessed article inclusion by examining titles and abstracts sequentially and in parallel, blinded to each other's ratings. Where there was disagreement between reviewers, the study in question was included for the next round of screening. Articles identified for full text screening were retrieved by searching online catalogues and university libraries. Where articles could not be retrieved, librarians were consulted and the authors were contacted with a request to provide the text. Two of a team of investigators (Paris Hosseini, Karrish Devan, Rebecca Whincup, Dory Ghanem, Aman Saini, Tomas Mastellari, Jack Fanshawe and Jonathan Rogers) assessed article inclusion by examining the full texts of the identified articles in parallel, blinded to each other's ratings. Where there was disagreement on the inclusion of a full text, an additional author who had not already reviewed the full text (Jonathan Rogers or Puja Mehta) arbitrated.

The systematic review is reported according to PRISMA guidelines with the PRISMA-DTA Checklist shown in Table 28 and the PRISMA-DTA for Abstracts Checklist in Table 29. The study protocol was preregistered with PROSPERO at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=239027.

Table 28: PRISMA-DTA checklist

Section/topic	#	PRISMA-DTA Checklist Item	Section where item is reported
TITLE / ABSTRACT			
Title	1	Identify the report as a systematic review (+/- meta-analysis)	6

		of diagnostic test accuracy (DTA) studies.	
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	6.1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2.8 6.2
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).	2.8 6.2
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).	6.2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6.3.2
Eligibility criteria	6	Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6.3.2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6.3.1
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.	Table 27
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6.3.2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6.3.3
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and	Table 30

		other characteristics (e.g. study design, clinical setting).	
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	6.3.4
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).	6.3.5
Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition. B) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards	6.3.5
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	6.3.5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6.3.5
RESULTS			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 9
Study characteristics	18	For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources	Table 33
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	Table 34
Results of individual studies	20	For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic	Figure 10

		accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.	
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	6.4.2 6.4.3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).	6.4.2 6.4.3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence.	6.5
Limitations	25	Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).	6.5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test).	6.5
FUNDING			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders.	6.3.6

Table 29: PRISMA-DTA for Abstracts Checklist

Section/topic	**#**	**PRISMA-DTA for Abstracts Checklist item**	**Location where item is reported**
TITLE and PURPOSE			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	6
Objectives	2	Indicate the research question, including components such as participants, index test, and target conditions.	6.1.1
METHODS			
Eligibility criteria	3	Include study characteristics used as criteria for eligibility.	6.1.2

Information sources	4	List the key databases searched and the search dates.	6.1.2
Risk of bias & applicability	5	Indicate the methods of assessing risk of bias and applicability.	6.1.2
Synthesis of results	A1	Indicate the methods for the data synthesis.	6.1.2
RESULTS			
Included studies	6	Indicate the number and type of included studies and the participants and relevant characteristics of the studies (including the reference standard).	6.1.3
Synthesis of results	7	Include the results for the analysis of diagnostic accuracy, preferably indicating the number of studies and participants. Describe test accuracy including variability; if meta-analysis was done, include summary results and confidence intervals.	6.1.3
DISCUSSION			
Strengths and limitations	9	Provide a brief summary of the strengths and limitations of the evidence	6.1.4
Interpretation	10	Provide a general interpretation of the results and the important implications.	6.1.4
OTHER			
Funding	11	Indicate the primary source of funding for the review.	6.1.5
Registration	12	Provide the registration number and the registry name	6.1.2

6.3.3 Data extraction

Where possible, data were sought at an individual patient level, but summary estimates were also included. Definitions of each variable for which the data were extracted are included in Table 30. Data were extracted by two of a group of investigators (Rebecca Whincup, Jack Fanshawe, Dory Ghanem, Benjamin Cross, Paris Hosseini, Karrish Devan, Aman Saini, Tomas Mastellari and Jonathan Rogers) in parallel, blinded to each other's data. Where there were discrepancies between the data extracted, a third author from this list arbitrated. In cases of ambiguity, the original investigators of the study were contacted for further details.

Table 30: Definitions of data extraction fields

Field	Definition

Citation	Per study metadata
Country	Country of affiliation of corresponding author
Study design	Clinical trial, cohort study, case-control study, cross-sectional study, case series or case report
IPD or aggregate data	IPD where any data can be extracted at the level of the individual patient. Otherwise, aggregate.
Number of patients represented by row	For IPD, this is 1. For aggregate data, this is the number of patients whose data has been aggregated.
Patient ID	Each patient in a study consecutively numbered.
Age	Age in years at the time of the EEG rounded down to the nearest integer.
Sex	As defined by study authors.
Ethnicity	Categories as defined by the UK Office for National Statistics. (Office for National Statistics, 2011)
Past neurological disorder affecting the brain (1/0)	1 if the patient has ever had a neurological disorder affecting the brain (i.e. excluding neurological disorders solely affecting the peripheral nervous system such as carpal tunnel syndrome). Otherwise, 0.
Past neurological disorder affecting the brain (specify)	If 1 for the above, specify which past neurological disorder(s) the patient has had.
Past psychiatric history (1/0)	1 if the patient has ever had a psychiatric disorder.
Past psychiatric history (specify)	If 1 for the above, specify which past psychiatric disorder(s) the patient has had.
Medications or drugs	List of names of all medications or drugs taken by the patient within the 7 days prior to the EEG.
Alcohol use	1 if the patient has used alcohol in the 7 days prior to the EEG.
Recreational drug use	1 if the patient has used recreational drugs in the 7 days prior to the EEG.
Benzodiazepine use	1 if the patient has used benzodiazepines in the 7 days prior to the EEG.
Antipsychotic use	1 if the patient has used antipsychotics in the 7 days prior to the EEG.
Antidepressant use	1 if the patient has used antipsychotics in the 7 days prior to the EEG.
Duration of catatonia	Duration in days of the catatonia prior to the EEG.
Catatonia meets DSM-5 criteria?	1 if either (a) the authors state that the patient meets DSM-5 criteria for catatonia or (b) there is evidence of at least 3 of the DSM-5 signs for catatonia in the report.
Periodic catatonia (author-defined)	1 if the report states that periodic catatonia was present
Type of EEG recording	Scalp or intracranial

EEG report		Verbatim copy of the report of the 1st EEG that a patient had during an episode of catatonia.
Final underlying diagnosis (multiple choice)		The category of disorder reported by the authors as underlying the catatonia: one of catatonia due to a general medical disorder, catatonia due to a primary psychotic disorder, catatonia due to a primary mood disorder or catatonia NOS. Catatonia NOS was used for psychiatric catatonia where the underlying diagnosis was unclear, the underlying diagnosis was other than a primary psychotic or mood disorder or catatonia was considered to be idiopathic.
Final underlying diagnosis (free text)		Specific diagnosis as given by the report
Duration of underlying illness		Time in days from start of underlying disorder until EEG. For a relapsing-remitting disorder, this is time since the first illness episode.
Treatments administered		List of all medications, neurostimulatory therapies and psychological therapies used to treat the catatonia, whether or not they were successful.
Outcome of catatonia		Full recovery (assumed if the patient was discharged from hospital and there was no other comment on outcome), partial recovery, continued catatonia or death during catatonia.
EEG coding	**EEG normal**	1 if EEG considered normal
	Features of encephalopathy	1 if features of encephalopathy (e.g. background slowing) present
	Posterior background frequency	Frequency of background rhythm in Hz
	Features of limbic encephalitis	1 if features of limbic encephalitis (e.g. extreme delta brush) present
	Reactive to eye opening	1 if background rhythm reactive to eye opening
	Any epileptiform discharges	1 if any epileptiform discharges present, including active seizure and interictal epileptiform discharges
	Focal abnormality	1 if any focal abnormality present
	Sleep recorded	1 if any period of sleep was recorded
	Sleep architecture normal	1 if sleep architecture noted to be normal
	Status epilepticus	1 if status epilepticus as defined by the Salzburg Criteria[4] is present.

IPD = individual participant data. NOS = not otherwise specified.

To uniformly synthesise the EEG findings, two neurophysiologists (Charles Fry and Franz Brunnhuber) developed a template with the following fields: whether the EEG was normal, the posterior background rhythm, the presence of features of encephalopathy, the presence of features of limbic encephalitis, whether the EEG was reactive to eye opening, the presence of epileptiform discharges, the presence of focal abnormalities, whether sleep was recorded, the presence of normal sleep architecture and the presence of status epilepticus. All EEG reports were coded using this template by a neurophysiologist (Charles Fry) and either a neurologist (Puja Mehta) or a psychiatrist (Jonathan Rogers) in parallel with blinding. Where there were discrepancies in the coding of EEG reports, one of the authors (Jonathan Rogers or Puja Mehta) who had not already reviewed the report arbitrated.

I decided to use the considered final clinical opinion of the report authors as the reference diagnostic standard. At its best, such a clinical diagnosis should integrate history, collateral history, physical examination findings and other investigations, as well as giving regard to the longitudinal course of the condition after the initial presentation. Given that there is a wide variety of potential causes for catatonia, and the diagnosis of psychiatric disorders remains largely clinical, this seemed to be the best option for a gold standard. Nonetheless, the quality of such clinical diagnosis is variable, so this was incorporated in the risk of bias assessment and the sensitivity analyses. Other options, such as an MRI scan, would rely on all possible general medical conditions having a clear neuroimaging correlate. Where catatonia was reported as having both a medical and psychiatric cause, it was coded as medical catatonia, as clinicians are most often interested in ruling out underlying medical conditions.

6.3.4 Risk of bias and applicability

For larger studies, the risk of bias was assessed using the QUADAS-2 tool, which is specifically designed for studies of diagnostic accuracy. (Whiting et al., 2011) The QUADAS-2 was independently completed by two investigators (Rebecca Whincup and Tomas Mastellari) and a third investigator (Jonathan Rogers) arbitrated where there were discrepancies. As recommended within the QUADAS-2 tool, I provided some review-specific guidance, which can be found in Table 31. Risk of bias for the smaller studies was assessed using a tool designed to assess the methodological quality of case series and case reports, (Murad et al., 2018) as many elements of the QUADAS-2 are unsuitable for smaller studies. This tool had two items that related specifically to studies of medication effects, so these items were excluded and the adapted tool with scoring criteria is in Table 32. Two of the investigators (Rebecca Whincup, Apoorva Vijay, Jack Fanshawe, Paris Hosseini, Benjamin Cross, Jonathan Rogers, Karrish Devan, Dory Ghanem, or Tomas Mastellari) conducted this assessment; in cases of discrepancies, a third author from this list arbitrated. The QUADAS-2 does not recommend using an overall rating, but for the tool used for smaller studies, a maximum score of 6 was possible, so scores of 0-2, 3-4, and 5-6 were denoted as low, moderate, and high quality, respectively.

Table 31: Adaptation of QUADAS-2 for quality assessment of larger studies (Whiting et al., 2011)

Domain	Signalling questions	Additional definitions
Patient selection	Was a consecutive or random sample of patients enrolled?	-
	Was a case-control design avoided?	A case-control design would be where subjects were selected on the basis of EEG findings, rather than on the basis of catatonia or an underlying diagnosis.
	Did the study avoid inappropriate exclusions?	Inappropriate exclusions would include difficult to diagnose patients or those with certain underlying conditions.
Index test	Were the index test results interpreted without knowledge of the results of the reference standard?	-
	If a threshold was used, was it prespecified?	-
	Could the conduct or interpretation of the index test have introduced bias?	-
Reference standard	Is the reference standard likely to correctly classify the target condition?	-
	Were the reference standard results interpreted without knowledge of the results of the index test?	-
Flow and timing	Was there an appropriate interval between index test and reference standard?	-
	Did all patients receive a reference standard?	-
	Did patients receive the same reference standard?	-
	Were all patients included in the analysis?	-

Table 32: Adaptation of quality assessment tool for smaller studies (Murad et al., 2018)the

Question	Definition of responses
1. Does the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?	1 – States that all patient(s) with a specified presentation are included in the article. 0 – States that not all patient(s) with a specified presentation are included in the article. 0 – Does not state
2. Was the exposure adequately ascertained?	1 – States that case(s) meet DSM-5 criteria for catatonia 1 – Evidence of at least 3 features of catatonia in DSM-5 definition (posturing, catalepsy, mutism, stereotypy, waxy flexibility, negativism, psychomotor agitation, stupor, mannerisms, grimacing, echopraxia, echolalia) 0 – Does not meet DSM-5 criteria for catatonia 0 – Unclear
3. Was the outcome adequately ascertained?	1 – EEG is described as abnormal and the specific abnormality is specified 1 – EEG is described as normal 0 – EEG is only described as abnormal (no details on type of abnormality)
4. Were other alternative causes that may explain the observation ruled out?	1 – Physical examination, blood tests and CT/MRI scan were performed, which either supported diagnosis or ruled out other explanations for catatonia and/or EEG findings. 0 – One or more of physical examination, blood tests and neuroimaging were not performed. 0 – Above tests were performed but did not rule out other explanations for catatonia and/or EEG findings.
7. Was follow-up long enough for outcomes to occur?	1 – Follow-up until recovery from catatonia, death or 1 year after onset of catatonia 0 – None of the above
8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?	1 – The following can all be ascertained: age, sex, past neurological history, past psychiatric history and final underlying diagnosis. If aggregate data, allow summary statistics (e.g. n female or mean age). 0 – At least one of the above cannot be ascertained

Where duplicate publications reporting the same individual were identified, the report with the most detail was included.

6.3.5 Data analysis

When designing this meta-analysis, I anticipated that there would be a few larger studies ($n \geq 5$), which would be suitable for a standard meta-analysis but would have little in the way of clinical details about patients that would be important for sensitivity analyses. It was important to include these studies, as the larger sample sizes meant they would be less susceptible to reporting bias.

In contrast, I anticipated that there would be many smaller studies ($n < 5$), which would likely exhibit reporting biases and be computationally unsuitable for standard meta-analysis but would have abundant clinical details about the patients. These would facilitate sensitivity and subgroup analyses using the characteristics of individual patients and their EEG results. I therefore decided to conduct two separate analyses:

1. The larger studies ($n \geq 5$) were synthesised based on summary estimates using formal meta-analysis methodology. Any sensitivity analyses where data were available were conducted on these larger studies.
2. The smaller studies ($n < 5$) were synthesised based on individual patient data as if they were all from one study using the binomial 'exact' method. The overall estimates of sensitivity and specificity might not be as reliable as the analysis of larger studies, but these studies could facilitate relevant sensitivity analyses and more detailed description of the patients.

Descriptive statistics for both types of studies were calculated and tabulated.

The primary outcome was whether an EEG was reported as abnormal, considered at a per-patient level. In this meta-analysis, an abnormal EEG was considered a positive finding, while a normal EEG was considered a negative finding. A true positive result would be a patient with medically caused catatonia who had an abnormal EEG. Secondary outcome measures were specific EEG abnormalities. The main measures of effect were sensitivity and specificity with 95% confidence intervals, which were presented using forest plots. The analysis was performed by using a bivariate random effects model of sensitivity and specificity. Unlike a usual univariate meta-analysis, which models only one outcome variable, the bivariate approach models sensitivity and specificity together. This is important because there tend to be explicitly or implicitly different thresholds for caseness across studies. Where, for example, a higher threshold is used, this would increase the specificity but reduce the sensitivity. To

generalise this point, sensitivity and specificity tend to be negatively correlated. The bivariate approach incorporates any such correlation into the model. (Reitsma et al., 2005)

This model allowed calculation of the area under the summary receiver operating characteristic (SROC) curve. Additional analyses were conducted to calculate positive predictive values, negative predictive values, and diagnostic likelihood ratios. These were used to generate a probability modifying plot, comparing pre-test and post-test probabilities. The calculation of positive predictive values and negative predictive values depends on the prevalence of medical catatonia among individuals with catatonia in a given population. A systematic review found that this prevalence varies by different treatment settings: medical catatonia accounted for 20% of catatonia overall, but among older adults in consultation-liaison psychiatry or critically ill patients, this figure was as high as 80%. (Oldham, 2018) I used 20% as an illustrative figure, but the probability modifying plots may be used for particular populations.

Psychotropic drugs have been associated with a wide range of EEG abnormalities. (Aiyer et al., 2016) I therefore performed a prespecified sensitivity analysis by excluding participants who used a psychotropic drug within 7 days prior to the EEG recording. Additional sensitivity analyses were conducted (for smaller studies or larger studies, as data permitted) by excluding certain studies or participants deemed to be at high risk of bias: studies published prior to 1980, studies published prior to 2010, studies not deemed of high quality, studies with concerns about the reference standard, studies where follow-up time was potentially inadequate to be confident in the final diagnosis, studies lacking either medical or psychiatric catatonia cases, individuals with a possible prior neurological disorder, individuals not meeting DSM-5 criteria for catatonia, individuals who were prescribed psychotropic medications (including benzodiazepines) in the 7 days prior to the EEG, individuals where alternative causes of catatonia had not been adequately ruled out, and individuals where the underlying disorder was neurodevelopmental. A prespecified subgroup analysis was conducted in which individuals were divided into age groups; the groups were children (<18 years), adults (18 – 64 years), and older adults (≥65 years). Additional subgroup analyses were conducted by sex and underlying diagnosis.

The meta-analysis was performed in Stata-MP v16.1 using the *midas* package. (Dwamena, 2007) The forest plot was produced using RevMan v5.4. Statistical significance was set at 0.05.

Study variability was assessed using the I^2 measure of heterogeneity and potential sources of heterogeneity were described and explored through subgroup analyses. Publication bias for the larger studies was assessed within the *midas* package by performing a linear regression of log odds ratios on the inverse root of effective sample sizes. (Dwamena et al., 2007)

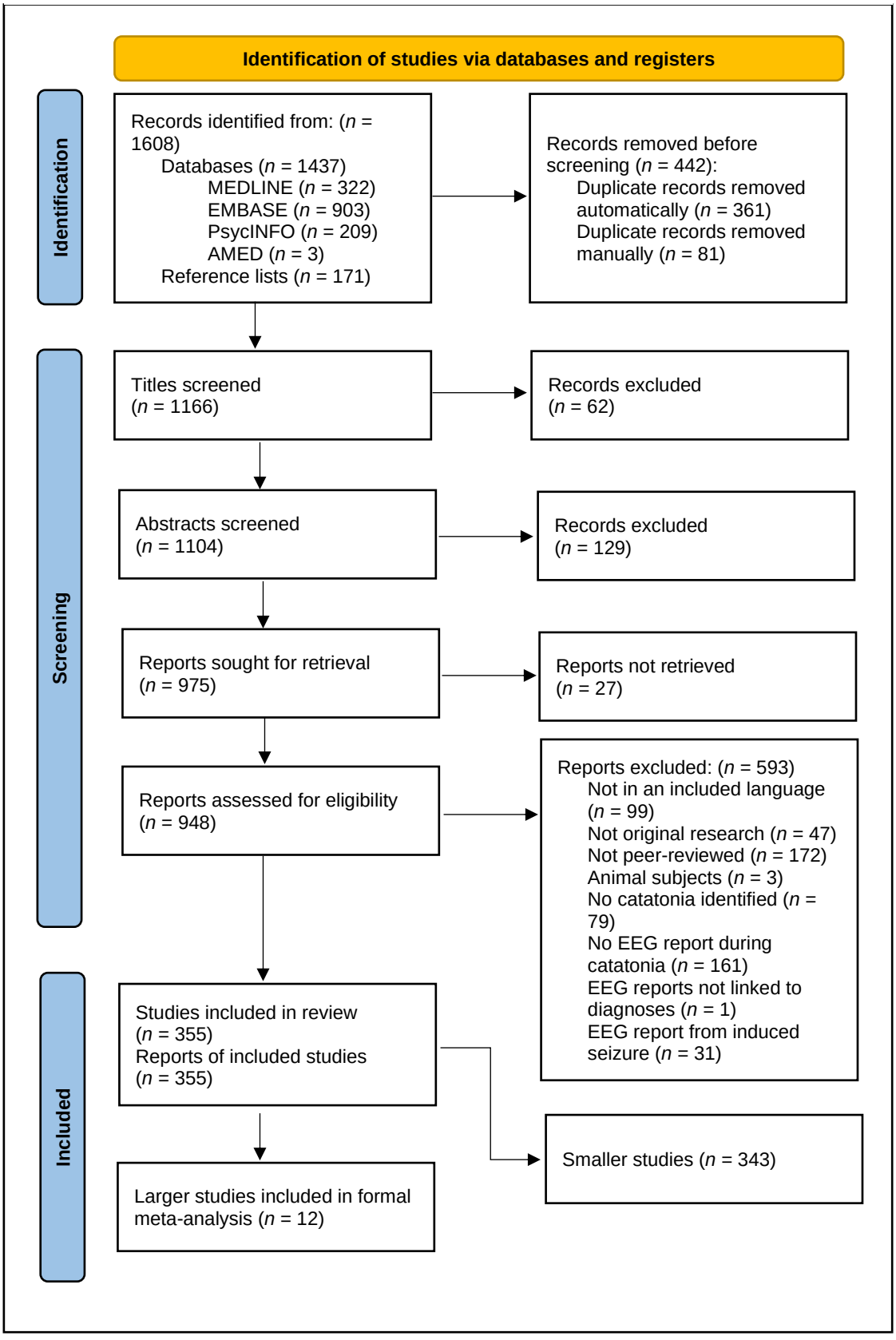
6.3.6 Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report or the decision to submit it for publication.

6.4 Results

The search strategy yielded 1608 results, which after deduplication left 1166 articles, which were screened (Figure 9). This resulted in 355 included studies with a total of 707 patients, of which 12 were larger studies ($n \geq 5$) and 343 were smaller studies ($n < 5$). All EEGs were recorded via the scalp; no studies reporting intracranial EEGs met the eligibility criteria.

Figure 9: PRISMA flowchart for study selection



6.4.1 Characteristics of included studies

The 12 larger studies are presented in Table 33. 6 were from the USA, 3 from the UK, and 1 each from Italy, Japan, and Mexico. There were 5 cohort studies and 7 case series. In total, 308 patients were included with a mean age of 48.2 years (*n*=139, SD = 8.9). Sex was reported in 161 patients, of whom 85 (52.8%) were male and 76 (47.2%) female. In terms of diagnostic groups, 99 had an underlying general medical condition, 11 a mood disorder, 137 a psychotic disorder, and 61 an unspecified psychiatric catatonia. The results for quality assessment of the larger studies using the QUADAS-2 tool are shown in Table 34.

Table 33: Characteristics of larger studies included in the meta-analysis

	Study	**Setting**	**Design**	**Sample size**	**Demographics**	***n* medical catatonia**	**Medical catatonia EEG findings**	***n* psychiatric catatonia**	**Psychiatric catatonia EEG findings**
1	MacMahon (1938)	UK; psychiatric hospital	Cohort	11	-	0	-	11	1 normal; 10 abnormal: delta rhythm (10)
2	Walter (1942)	UK; psychiatric hospital	Cohort	6	-	0	-	6	3 normal; 1 doubtful (considered normal for meta-analysis); 2 abnormal
3	Stevens (1958)	USA; psychiatric hospital	Case series	21	-	0	-	21	20 normal; 1 abnormal: runs of high-voltage activity (1)
4	Ishibashi (1963)	Japan; psychiatric hospital	Case series	11	-	0	-	11	1 normal; 8 borderline (considered normal for meta-analysis); 2 abnormal

5	Abenson (1970)	UK; psychiatric hospital	Cohort	79	-	0	-	79	60 normal; 19 abnormal: 'choppy' abnormalities (9), temporal (focal) abnormalities (7), dysrhythmic abnormalities (3)
6	Philbrick (1994)	USA; general hospital	Case series	5	3 M, 2 F Age 59.6 (mean), 16.2 (SD)	0	-	5	4 normal; 1 abnormal: background slowing (1)
7	Carroll (1995)	USA; psychiatric hospital or medical psychiatry unit	Case series	26	15 M, 11 F Age 48.2 (mean), 21.4 (SD)	13	2 normal; 11 abnormal: diffuse slowing (8), focal slowing (2), bilateral spikes (1)	13	8 normal; 5 abnormal: diffuse slowing (4), focal slowing (1)
8	Carroll (1998)	USA; psychiatric hospital	Case series	12	Age 41.8 (mean), 17.9 (SD)	6	1 normal; 5 abnormal	6	5 normal; 1 abnormal
9	Smith (2012)	USA; general hospital	Cohort	68	28 M, 40 F Age 51.9 (mean), 20.9 (SD)	16	1 normal; 15 abnormal: diffuse slowing (13), focal temporal slowing (5), asymmetry (6)*	52	13 normal; 39 abnormal: diffuse slowing (31), focal temporal slowing (7), asymmetry (6)*
10	Llesuy (2017)	USA; general hospital	Case series	20	Age 49.6 (mean), 17.7 (SD)	18	7 normal; 11 abnormal: generalised slowing (7), generalised slowing with epileptiform activity (3), seizures (1)	2	1 normal; 1 abnormal: generalised slowing (1)

11	Espinola-Nadurille (2019)	Mexico; neurosciences hospital	Cohort	41	-	41	4 normal; 37 abnormal: generalised dysfunction (33), asymmetric activity (7), delta-brush activity (7), epileptic activity (6), focal dysfunction (3)*	0	-
12	Ursitti (2021)	Italy; children's hospital	Case series	8	3 M, 5 F Age 15.1 (mean), 1.6 (SD)	5	1 normal; 4 abnormal: focal slowing (3), status epilepticus (1), diffuse beta activity (1)*	3	2 normal; 1 abnormal: focal slowing (1)*

*Each patient may be reported to have more than one EEG abnormality in these studies.

Table 34: Funding statements and quality assessment of larger studies using QUADAS-2

	Study	**Funding**	**Risk of Bias**				**Applicability Concerns**		
			Patient Selection	**Index Test**	**Reference Standard**	**Flow and Timing**	**Patient Selection**	**Index Test**	**Reference Standard**
1	MacMahon (1938)	Not stated	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
2	Walter (1942)	Not stated	Low	Low	Unclear	Unclear	Low	High	Low
3	Stevens (1958)	Not stated	High	Low	Low	Unclear	High	Low	High
4	Ishibashi (1963)	Not stated	High	Unclear	Unclear	High	Low	Unclear	Unclear
5	Abenson (1970)	Not stated	Low	Low	Low	Unclear	Low	Low	Low
6	Philbrick (1994)	Not stated	High	Unclear	Low	Low	High	Unclear	High

7	Carroll (1995)	Not stated	Low	Low	High	Unclear	Low	Low	Low
8	Carroll (1998)	Not stated	Low	Unclear	High	High	Low	Unclear	Low
9	Smith (2012)	Non-commercial support*	Low	Low	Low	High	Low	Low	Low
10	Llesuy (2017)	Not stated	Low	Unclear	Low	High	Low	Low	Low
11	Espinola-Nadurille (2019)	None	Low	Unclear	Low	Low	High	Low	Low
12	Ursitti (2021)	None	High	Unclear	Unclear	Low	Low	Low	Low

*Study was partially supported by the Center for Translational Science Activities at Mayo Clinic. The Center was funded in part by a grant from the National Center for Research Resources, a component of the National Institutes of Health (NIH).

Among the 343 smaller studies, there were 399 patients, of whom 302 had medical catatonia and 97 psychiatric catatonia. A summary of the smaller studies and the cases in them is presented in Table 35. The diagnoses and treatments administered in these cases are shown in Table 36 and Table 37 respectively.

Table 35: Characteristics of smaller studies and of patients in smaller studies

Study characteristics	**All studies (*K*=343)**
Publication year, min, max	1952, 2022
Country of corresponding author, *k* (%)	
- **USA**	134 (39.1)
- **Japan**	23 (6.7)
- **India**	22 (6.4)
- **Germany**	15 (4.4)
- **Italy**	15 (4.4)
- **UK**	14 (4.1)
- **France**	13 (3.8)
- **Other**	107 (31.2)
Study design, *k* (%)	
- **Cohort study**	4 (1.2)
- **Case series**	66 (19.2)
- **Case report**	273 (79.6)
Number of patients, *k* (%)	

- **1**	308 (89.8)		
- **2**	17 (5.0)		
- **3**	15 (4.4)		
- **4**	3 (0.9)		
Quality assessment, *k* (%)			
- **Patient(s) represent(s) the whole experience of the investigator (centre)**	205 (59.8)		
- **Exposure adequately ascertained?**	234 (68.2)		
- **Outcome adequately ascertained?**	334 (97.4)		
- **Other alternative causes that may explain the observation ruled out?**	128 (37.3)		
- **Follow-up long enough for outcomes to occur?**	185 (53.9)		
- **Case(s) described with sufficient details?**	262 (76.4)		
Overall study quality rating, *k* (%)			
- **Low**	41 (12.0)		
- **Moderate**	184 (53.6)		
- **High**	118 (34.4)		
<u>Patient characteristics</u>	**Medical catatonia (*N*=302)**	**Psychiatric catatonia (*N*=97)**	**Total (*N*=399)**
Sex, *n* (%)			
- **Male**	123 (40.7)	49 (50.5)	172 (43.1)
- **Female**	178 (58.9)	47 (48.5)	225 (56.4)
- **Not specified**	1 (0.3)	1 (1.0)	2 (0.5)
Age / years, mean (SD)	35.9 (19.8)	37.8 (20.8)	36.4 (20.0)
Ethnicity, *n* (%)			
- **Asian**	15 (5.0)	6 (6.2)	21 (5.3)
- **Black**	15 (5.0)	5 (5.2)	20 (5.0)
- **White**	32 (10.6)	15 (15.5)	47 (11.8)
- **Other**	11 (3.6)	1 (1.0)	12 (3.0)
- **Not specified**	229 (75.8)	70 (72.2)	299 (74.9)
Prior neurological history affecting brain, *n* (%)			
- **Present**	80 (26.5)	17 (17.5)	97 (24.3)
- **Absent**	212 (70.2)	75 (77.3)	287 (71.9)
- **Not stated**	10 (3.3)	5 (5.2)	15 (3.8)
Prior psychiatric history, *n* (%)			
- **Present**	113 (37.4)	64 (66.0)	177 (44.4)
- **Absent**	181 (60.0)	29 (29.9)	210 (52.6)
- **Not stated**	8 (2.7)	4 (4.1)	12 (3.0)
Medication and drug use mentioned in 7 days prior to EEG, *n* (%)			
- **Alcohol**	3 (1.0)	1 (1.0)	4 (1.0)

- **Recreational drugs (not alcohol)**	13 (4.3)	0 (0.0)	13 (3.3)
- **Antidepressants**	22 (7.3)	10 (10.3)	32 (8.0)
- **Antipsychotics**	104 (34.4)	31 (32.0)	135 (33.8)
- **Benzodiazepines**	79 (26.2)	18 (18.6)	97 (24.3)
Catatonia meeting DSM-5 criteria, *n* (%)	227 (75.2)	70 (72.2)	297 (74.4)
Catatonia duration prior to EEG / days (*n* = 174)			
- **Mean (SD)**	21.5 (47.8)	36.7 (93.1)	24.4 (59.2)
- **Median (IQR)**	7 (2 – 21)	14 (2 – 36)	7 (2 – 28)
Periodic catatonia (as identified by authors), *n* (%)	2 (0.7)	9 (9.3)	11 (2.8)
Underlying diagnosis, *n* (%)			
- **Catatonia due to a general medical disorder**	302 (100.0)	-	302 (75.7)
- **Catatonia due to a primary psychotic disorder**	-	44 (45.4)	44 (11.0)
- **Catatonia due to a primary mood disorder**	-	24 (24.7)	24 (6.0)
- **Catatonia NOS***	-	29 (29.9)	29 (7.3)
Duration of underlying illness prior to EEG / days (*n* = 266)			
- **Mean (SD)**	515 (1985)	1616 (3377)	755 (2396)
- **Median (IQR)**	65 (14 – 1095)	65 (14 – 1095)	28 (10 – 150)
Clinical outcome of catatonia, *n* (%)			
- **Full recovery**	236 (78.2)	73 (75.3)	309 (77.4)
- **Partial recovery**	25 (8.3)	15 (15.5)	40 (10.0)
- **Continued catatonia**	10 (3.3)	4 (4.1)	14 (3.5)
- **Death**	22 (7.3)	0 (0.0)	22 (5.5)
- **Not stated**	9 (3.0)	5 (5.2)	14 (3.5)

IQR = interquartile range. NOS = not otherwise specified. SD = standard deviation.

*This category was used for psychiatric catatonia where the underlying diagnosis was unclear, the underlying diagnosis was other than a primary psychotic or mood disorder, or catatonia was considered idiopathic.

Table 36: Diagnostic groups of cases in smaller studies

Category (*N*=399)	***n* (%)**
Catatonia due to a general medical condition	302 (75.7)
- **Autoimmune encephalitis**	- 98 (24.6)
- **CNS structural abnormality**	- 8 (2.0)
- **CNS tumour**	- 3 (0.8)
- **Cerebrovascular**	- 9 (2.3)
- **Dementia / cognitive impairment**	- 6 (1.5)
- **Drug withdrawal-related**	- 14 (3.5)
- **Drug-induced**	- 23 (5.8)
- **Encephalitis, unspecified**	- 2 (0.5)

- **Encephalitis lethargica**	- 4 (1.0)
- **Encephalopathy, hypoxic-ischaemic**	- 3 (0.8)
- **Encephalopathy, thyroid-related**	- 5 (1.3)
- **General medical condition, unspecified**	- 6 (1.5)
- **HIV-related**	- 2 (0.5)
- **Infective encephalitis**	- 17 (4.3)
- **Metabolic**	- 10 (2.5)
- **Miscellaneous**	- 23 (5.8)
- **Neuroleptic malignant syndrome**	- 12 (3.0)
- **Prion**	- 9 (2.3)
- **Systemic lupus erythematosus**	- 8 (2.0)
- **Seizure-related**	- 36 (9.0)
- **Toxin-induced**	- 4 (1.0)
Catatonia due to a primary psychotic disorder	44 (11.0)
- **Catatonic schizophrenia**	- 3 (0.8)
- **Paranoid schizophrenia**	- 1 (0.3)
- **Primary psychotic disorder, unspecified**	- 9 (2.3)
- **Schizoaffective disorder**	- 4 (1.0)
- **Schizophrenia, unspecified**	- 26 (6.5)
- **Schizophreniform disorder**	- 1 (0.3)
Catatonia due to a primary mood disorder	24 (6.0)
- **Bipolar affective disorder**	- 10 (2.5)
- **Major depressive disorder**	- 13 (3.3)
- **Primary mood disorder, unspecified**	- 1 (0.3)
Catatonia not otherwise specified	29 (7.3)
- **Anxiety disorder**	- 1 (0.3)
- **Autism spectrum disorder**	- 7 (1.8)
- **Idiopathic catatonia**	- 6 (1.5)
- **Obsessive compulsive disorder**	- 1 (0.3)
- **Periodic catatonia**	- 2 (0.5)
- **Primary psychiatric disorder, unspecified**	- 12 (3.0)

Table 37: Treatments administered in smaller studies

Treatment (*N*=399)	***n* (%) ***
Benzodiazepine	206 (51.6)
Antipsychotic	144 (36.1)

Immunotherapy	109 (27.3)
Electroconvulsive therapy	102 (25.6)
Anticonvulsant	92 (23.1)
Antidepressant	40 (10.0)
Antibiotic	35 (8.8)
Dopamine agonist or precursor	21 (5.3)
Surgical intervention	19 (4.8)
Anticholinergic	16 (4.0)
Glutamatergic therapies (amantadine, memantine, ketamine)	14 (3.5)
Barbiturate	12 (3.0)
Lithium	12 (3.0)
Stimulant	5 (1.3)
'Z-drug'	5 (1.3)
Psychological therapy	4 (1.0)
Antihistamine	3 (0.8)
Reserpine	2 (0.5)
tDCS or rTMS	2 (0.5)

* In many cases, patients received multiple treatments, so treatment categories are not mutually exclusive

6.4.2 Diagnostic test accuracy of the larger included studies

Figure 10 displays a forest plot for the sensitivity and specificity of the larger studies alongside the raw data. Of note, 6 studies included only patients with psychiatric catatonia, (Abenson, 1970; Ishibashi et al., 1963; MacMahon and Walter, 1938; Philbrick and Rummans, 1994; Stevens and Derbyshire, 1958; Walter, 1942) so sensitivity cannot be derived for these studies, while 1 study included only patients with medical catatonia, (Espinola-Nadurille et al., 2019) so specificity cannot be derived for this study.

The main diagnostic test accuracy meta-analysis found that the sensitivity (i.e., the proportion of patients with medical catatonia who had an abnormal EEG) was 0.82 (95% CI 0.67 to 0.91) and the specificity (i.e., the proportion of patients with psychiatric catatonia who had a normal EEG) was 0.66 (95% CI 0.45 to 0.82). The proportion of variance accounted for by between-study heterogeneity was measured with an I^2 statistic of 74% (95% CI 42 to 100%). The positive likelihood ratio was 2.4 (95% CI 1.4 to 4.1) and the negative likelihood ratio was 0.28 (95% CI 0.15 to 0.51). The diagnostic odds ratio (the ratio of the odds of having an abnormal EEG in those with an underlying medical condition compared to the odds in those with an underlying psychiatric disorder) was 9 (95% CI 3 to 22). A summary receiver operating characteristics (SROC) curve displaying this result along with the 5 studies

from which both sensitivity and specificity could be derived is shown in Figure 11 with an area under the SROC curve of 0.83 (95% CI 0.79 to 0.86), corresponding to excellent discrimination. (Hosmer et al., 2013) Study 10 (Llesuy et al., 2017) appears to be an outlier in Figure 11, but its specificity is based on findings in only 2 patients, so it has a wide confidence interval, as shown in Figure 10. For clinical interpretation, Figure 12 displays a probability modifying plot, which illustrates the effect on the post-test probability of medical catatonia of an abnormal (positive) or normal (negative) EEG for a given prior probability. If a prevalence of medical catatonia among all cases of catatonia of 20% is assumed, (Oldham, 2018) the positive predictive value is 0.37 and the negative predictive value is 0.93. Fagan's Bayesian nomogram assuming a baseline probability of medical catatonia of 20% is shown in Figure 13.

Figure 10: Forest plot of sensitivity and specificity of larger studies

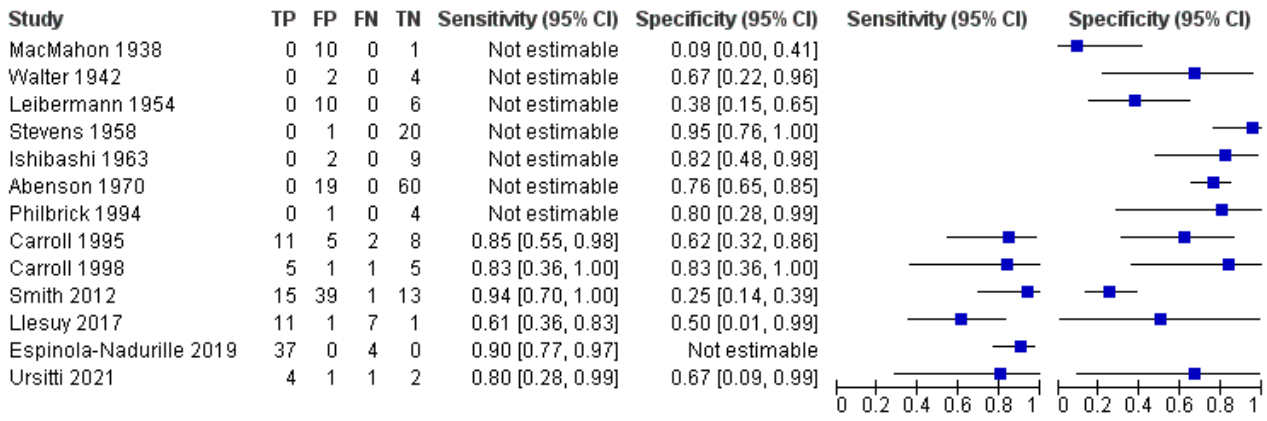


Figure 11: Summary receiver operator characteristics (ROC) curve for larger studies

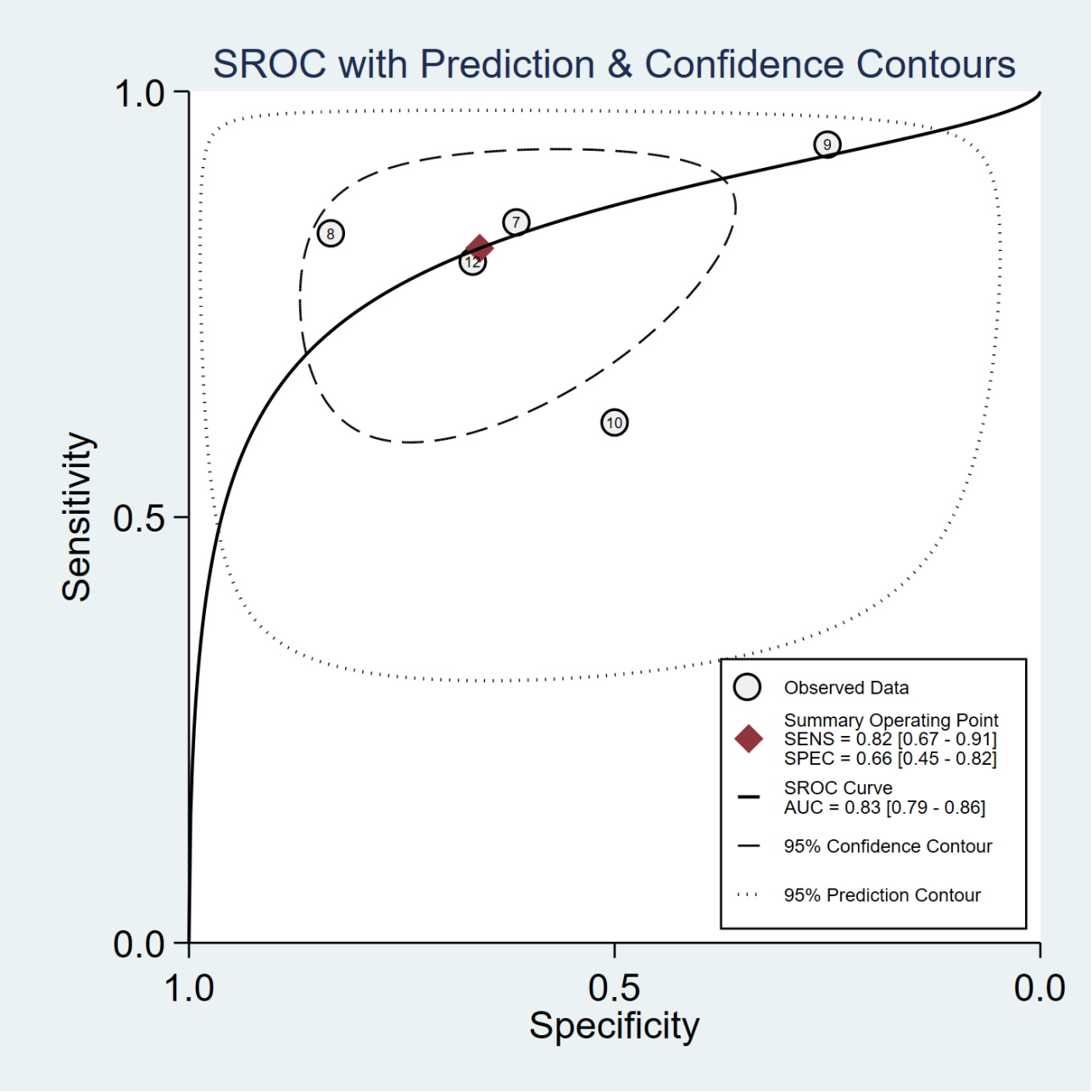


Figure 12: Probability modifying plot for interpretation of EEG findings in catatonia

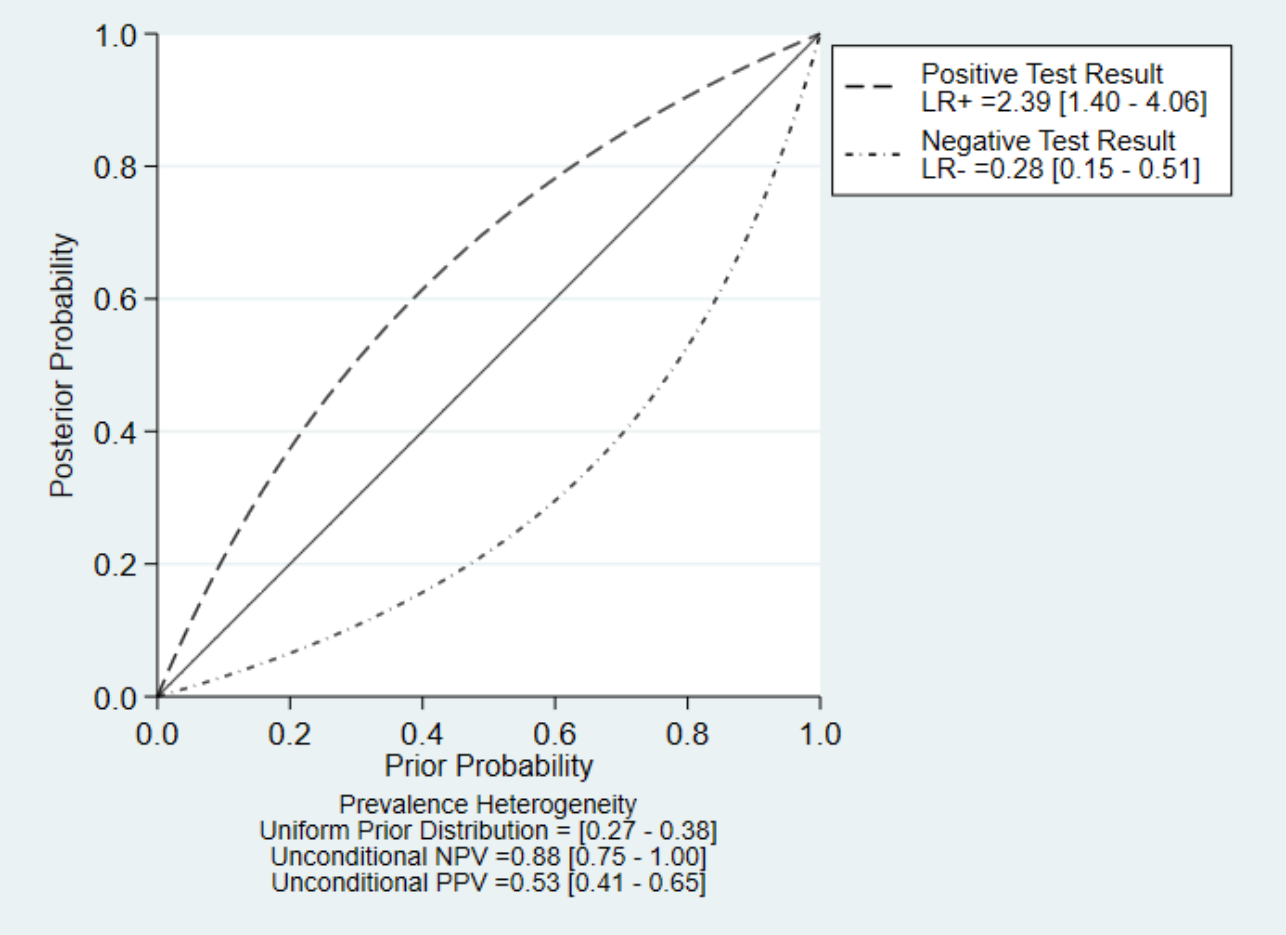
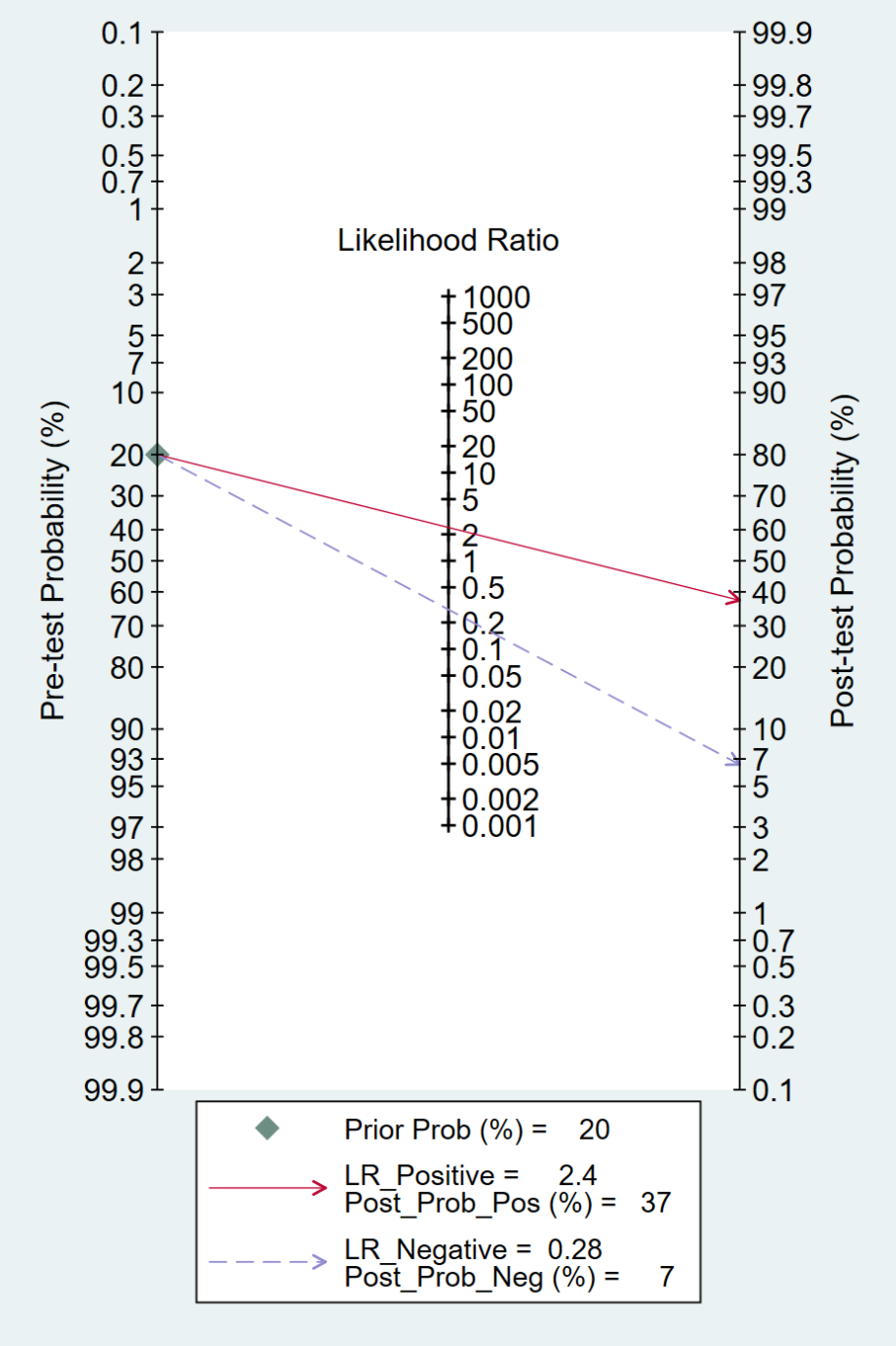


Figure 13: Fagan's Bayesian nomogram for meta-analysis of larger studies



Model diagnostics for the larger studies are shown in Figure 14, which shows a good model fit without any outliers. No studies were considered influential based on their Cook's distance. When publication bias was assessed by performing a linear regression of log odds ratios on the inverse root of effective sample sizes, no evidence for publication bias was found with a regression coefficient of 0.9 (95% CI -13.6 to 15.4), as illustrated by the funnel plot in Figure 15. Sensitivity analyses excluding studies that were older, had more concerns on the QUADAS-2, had high concerns about the reference standard or

lacked both medical and psychiatric catatonia cases were performed with the results shown in Table 38.

Figure 14: Model diagnostics for meta-analysis of larger studies

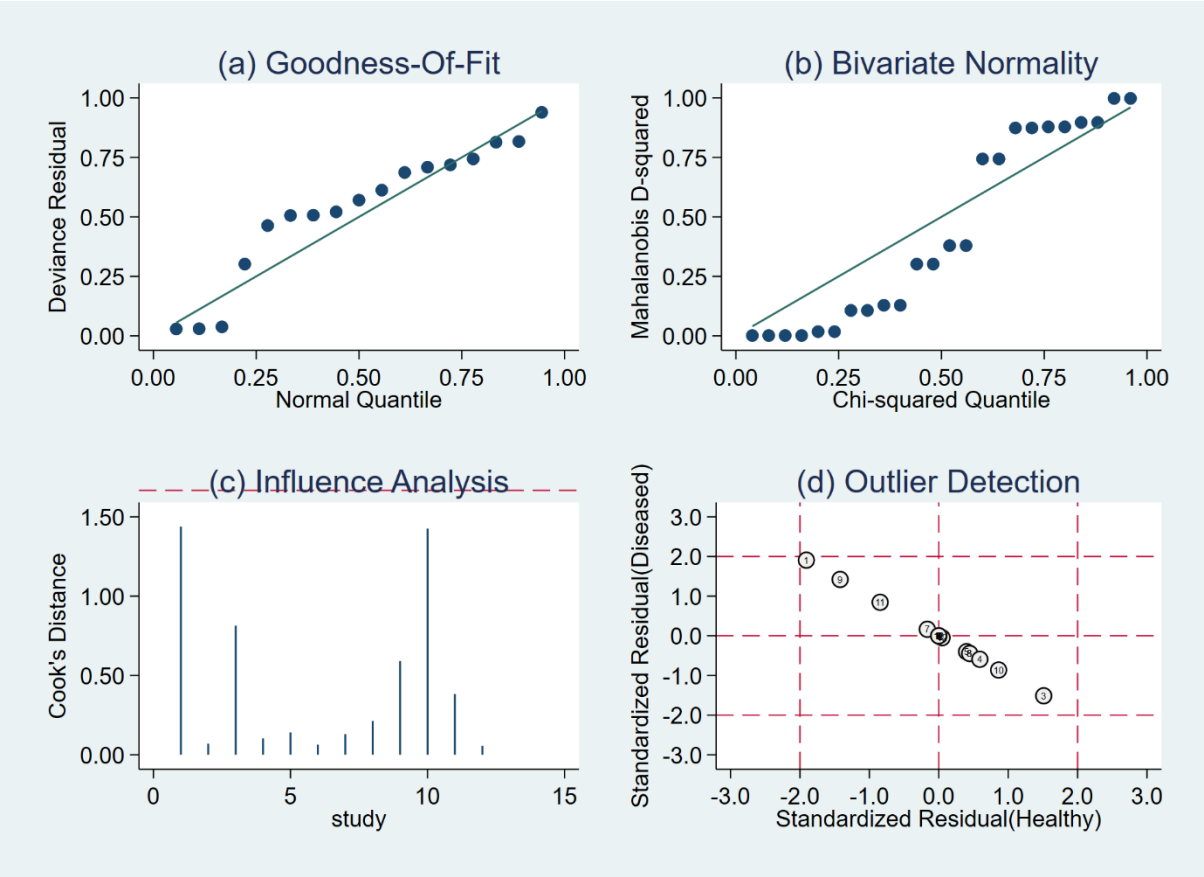


Figure 15: Funnel plot for publication bias of larger studies

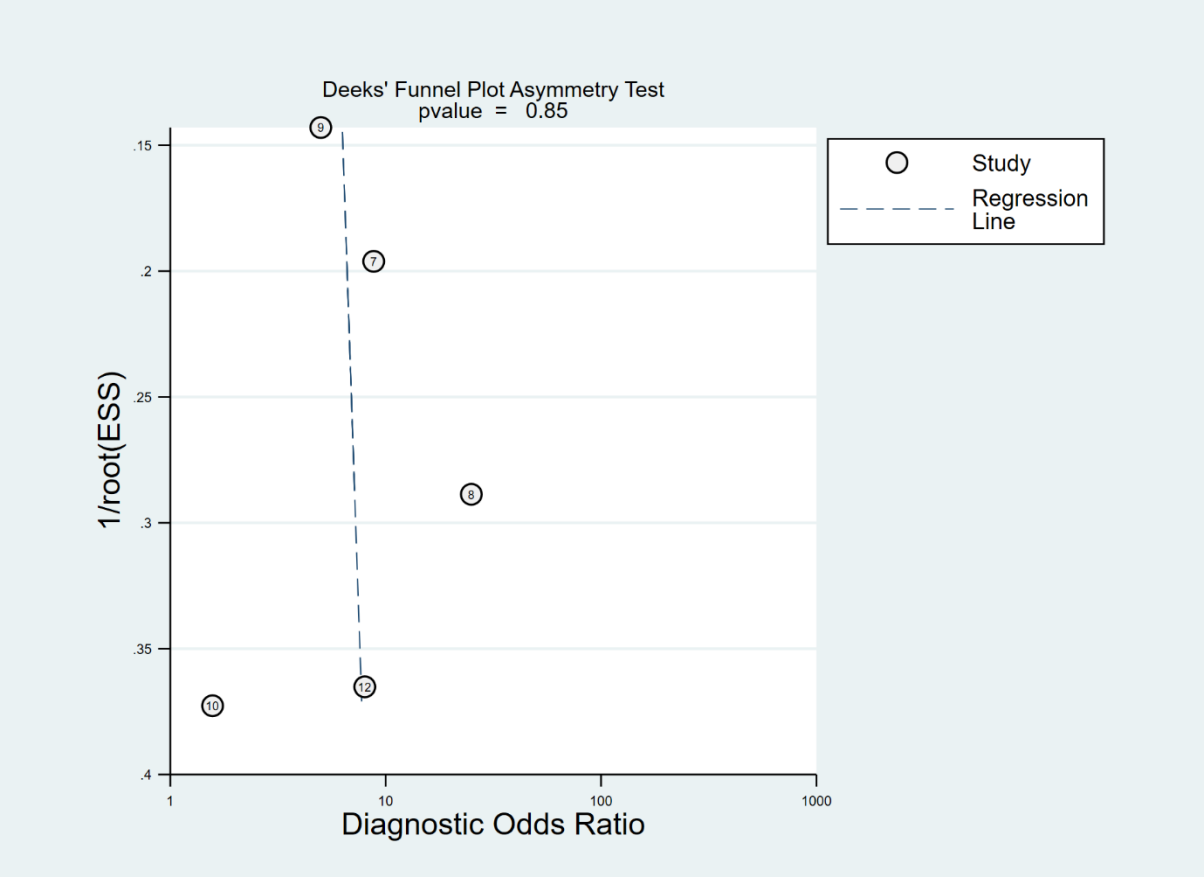


Table 38: Sensitivity analyses for larger studies

Analysis	Number of studies (*k*)	Number of subjects (*n*)	Sensitivity (95% CI)	Specificity (95% CI)	Area under ROC curve (95% CI)	I^2
Primary analysis	12	308	0.82 (0.67 to 0.91)	0.66 (0.45 to 0.82)	0.83 (0.79 to 0.86)	0.74
Only studies published from 1980 onwards	7	180	0.83 (0.69 to 0.91)	0.58 (0.34 to 0.78)	0.80 (0.76 to 0.83)	0.64
Only studies with low concerns in at least 5 domains of QUADAS-2	5	234	0.82 (0.64 to 0.92)	0.55 (0.31 to 0.76)	0.77 (0.73 to 0.81)	0.59
Only studies with low concerns about reference standard	6	234	0.76 (0.45 to 0.93)	0.69 (0.38 to 0.89)	0.79 (0.75 to 0.82)	0.62
Only studies containing both medical and psychiatric catatonia cases	5	134	0.80 (0.63 to 0.91)	0.56 (0.31 to 0.79)	0.77 (0.73 to 0.81)	0.62

6.4.3 Diagnostic test accuracy of the smaller included studies

The results of the EEG findings for the smaller studies are shown combined in a 2x2 table (Table 39). From this table, the sensitivity was 0.76 (95% CI 0.71 to 0.81) and the specificity was 0.67 (0.57 to 0.76). The area under the ROC curve was 0.71 (95% CI 0.67 to 0.76). Sensitivity analyses excluding the following groups were conducted and the results are shown in Table 40: studies published prior to 1980, studies not deemed of high quality, studies where follow-up time was potentially inadequate to be confident in the final diagnosis, studies where alternative causes were not adequately ruled out, individuals with a possible prior neurological disorder, individuals with psychotropic drug use within 7 days prior to the EEG, individuals not meeting DSM-5 criteria for catatonia and individuals where the underlying disorder was neurodevelopmental. There was substantial overlap in the confidence intervals for sensitivity and specificity with the primary analysis for all sensitivity analyses, suggesting that the results were robust to the exclusion of studies at high risk of bias. The number of abnormal EEGs by underlying diagnosis are presented in Table 41. Subgroup analyses by age, sex, diagnostic subgroup and continent of participants are shown in Table 42. Subgrouping by age merits particular attention: while the area under the ROC curve for children (0.79 [95% CI 0.68 to 0.87]) and adults (0.72 [95% CI 0.66 to 0.77]) provided acceptable discrimination, for older adults (0.53 [95% CI 0.36 to 0.68]) the EEG effectively provided no discrimination between medical and psychiatric catatonia. (Hosmer et al., 2013)

Table 39: EEG results by specific EEG abnormality for smaller studies

	Medical catatonia (*N*=302)	**Psychiatric catatonia (*N*=97)**
EEG normal, *n* (%)	***False negatives*** 72 (23.8)	***True negatives*** 65 (67.0)
EEG abnormal, *n* (%)*	***True positives*** 230 (76.2)	***False positives*** 32 (33.0)
- **Features of encephalopathy**	- 160 (53.0)	- 22 (22.7)
- **Features of limbic encephalitis**	- 8 (2.6)	- 0 (0.0)
- **Epileptiform discharges**	- 75 (24.8)	- 6 (6.2)
- **Focal abnormality**	- 73 (24.2)	- 5 (5.2)
- **Status epilepticus present**	- 28 (9.3)	- 0 (0.0)

*Some EEGs had more than one abnormality, so figures on the types of abnormalities add up to more than the total number of abnormal EEGs.

Table 40: Sensitivity analyses for smaller studies

Analysis	*N*	Sensitivity (95% CI)	Specificity (95% CI)	Area under ROC curve (95% CI)
Primary analysis	399	0.76 (0.71 to 0.81)	0.67 (0.57 to 0.76)	0.72 (0.67 to 0.76)
Excl. studies published prior to 1980	354	0.75 (0.69 to 0.80)	0.75 (0.64 to 0.84)	0.75 (0.70 to 0.79)
Excl. studies published prior to 2010	246	0.73 (0.67 to 0.80)	0.74 (0.60 to 0.85)	0.74 (0.68 to 0.79)
Excl. studies where quality is not high	127	0.77 (0.68 to 0.85)	0.77 (0.55 to 0.92)	0.77 (0.69 to 0.84)
Excl. studies where follow-up time was inadequate*	202	0.74 (0.66 to 0.80)	0.74 (0.56 to 0.87)	0.74 (0.67 to 0.80)
Excl. studies where alternative causes were not adequately ruled out	134	0.75 (0.66 to 0.83)	0.80 (0.59 to 0.93)	0.78 (0.70 to 0.84)
Excl. individuals with a possible past neurological disorder	287	0.72 (0.66 to 0.78)	0.63 (0.51 to 0.74)	0.67 (0.61 to 0.73)
Excl. individuals with psychotropic drug use †	212	0.79 (0.72 to 0.85)	0.65 (0.52 to 0.78)	0.72 (0.66 to 0.78)
Excl. individuals not meeting DSM-5 criteria for catatonia	297	0.74 (0.68 to 0.80)	0.70 (0.58 to 0.80)	0.72 (0.67 to 0.77)
Excl. individuals where underlying disorder is neurodevelopmental	392	0.76 (0.71 to 0.81)	0.67 (0.56 to 0.76)	0.71 (0.67 to 0.76)

*Item 7 of QUADAS-2, defined for this study as follow-up until recovery from catatonia, death or one year after onset of catatonia.

† Defined as antidepressants, antipsychotics, benzodiazepines, alcohol or recreational drugs within 1 week prior to EEG.

Table 41: EEG abnormalities by diagnostic group for smaller studies

Underlying diagnosis	EEG normal, *n* (%)	EEG abnormal, *n* (%)	Total
Catatonia due to a general medical condition	72 (23.8)	230 (76.2)	302
Catatonia due to a primary psychotic disorder	32 (72.7)	12 (27.3)	44
Catatonia due to a primary mood disorder	15 (62.5)	9 (37.5)	24
Catatonia NOS	18 (62.1)	11 (37.9)	29

Table 42: Subgroup analyses for smaller studies

Analysis	*N*	Sensitivity (95% CI)	Specificity (95% CI)	Area under ROC curve (95% CI)
Primary analysis	399	0.76 (0.71 to 0.81)	0.67 (0.57 to 0.76)	0.72 (0.67 to 0.76)
Subgroup by age				
- **Children (0 – 17 years)**	83	0.78 (0.66 to 0.87)	0.79 (0.54 to 0.94)	0.79 (0.68 to 0.87)
- **Adults (18 – 64 years)**	271	0.76 (0.70 to 0.82)	0.68 (0.55 to 0.79)	0.72 (0.66 to 0.77)
- **Older adults (65+ years)**	40	0.69 (0.49 to 0.85)	0.36 (0.11 to 0.69	0.53 (0.36 to 0.68)
Subgroup by sex				
- Male	172	0.74 (0.65 to 0.81)	0.69 (0.55 to 0.82)	0.72 (0.64 to 0.78)
- Female	225	0.78 (0.71 to 0.83)	0.64 (0.49 to 0.77)	0.71 (0.64 to 0.77)
Subgroup by diagnostic group				
- Catatonia due to a GMC vs catatonia due to a primary psychotic disorder	346	0.76 (0.71 to 0.81)	0.73 (0.57 to 0.85)	0.74 (0.70 to 0.79)
- Catatonia due to a GMC vs catatonia due to a primary mood disorder	326	0.76 (0.71 to 0.81)	0.63 (0.41 to 0.81)	0.69 (0.64 to 0.74)
- Catatonia due to a GMC vs catatonia NOS	331	0.76 (0.71 to 0.81)	0.62 (0.42 to 0.79)	0.69 (0.64 to 0.74)
Subgroup by continent				
- **North America**	174	0.79 (0.71 to 0.85)	0.68 (0.50 to 0.82)	0.73 (0.66 to 0.79)
- **Europe**	117	0.68 (0.57 to 0.78)	0.60 (0.42 to 0.76)	0.64 (0.55 to 0.73)
- **Asia**	86	0.81 (0.70 to 0.89)	0.72 (0.47 to 0.90)	0.77 (0.66 to 0.85)

GMC – general medical condition. NOS – not otherwise specified.

As a secondary analysis among the smaller studies, I examined the diagnostic accuracy of each individual EEG abnormality, as shown in Table 43. Features of limbic encephalitis, epileptiform discharges, focal abnormalities, and status epilepticus were all highly specific with varying sensitivity,

but the features of encephalopathy were more sensitive and much less specific. The EEG posterior background frequencies were not usually specified but the available frequencies are presented in Table 44.

Table 43: Diagnostic test accuracy by individual EEG abnormality for smaller studies

EEG abnormality*	Sensitivity (95% CI)	Specificity (95% CI)	Area under the ROC curve (95% CI)
Any abnormality (primary analysis)	0.76 (0.71 to 0.81)	0.67 (0.57 to 0.76)	0.71 (0.67 to 0.76)
Features of encephalopathy	0.58 (0.52 to 0.64)	0.77 (0.68 to 0.85)	0.68 (0.63 to 0.73)
Features of limbic encephalitis	0.03 (0.01 to 0.05)	1.00 (0.96 to 1.00)	0.51 (0.46 to 0.56)
Epileptiform discharges	0.25 (0.20 to 0.30)	0.94 (0.87 to 0.98)	0.59 (0.54 to 0.64)
Focal abnormality	0.24 (0.20 to 0.30)	0.95 (0.88 to 0.98)	0.60 (0.55 to 0.65)
Status epilepticus	0.09 (0.06 to 0.13)	1.00 (0.96 to 1.00)	0.55 (0.50 to 0.60)

*Categories of abnormalities are not mutually exclusive, as many EEGs showed more than one abnormality.

Table 44: EEG posterior background frequencies for smaller studies

Background frequency range (Kane et al., 2017)	*n* (%)
Delta (0.1 – <4 Hz)	23 (5.8)
Delta-theta (0.1 – <8 Hz)	21 (5.3)
Theta (4 – <8Hz)	23 (5.8)
Theta-alpha (4 – 13 Hz)	2 (0.5)
Slowing unspecified	81 (20.3)
Alpha (8 – 13 Hz)	13 (3.3)
Not stated	236 (59.2)

6.5 Discussion

In this systematic review and meta-analysis of diagnostic test accuracy, including 355 studies and 707 patients, I found that scalp EEG has excellent discrimination in ascertaining whether catatonia is due to a medical cause in larger studies with acceptable discrimination in smaller studies. This result was robust to excluding studies at high risk of bias.

EEG performance varied across age groups with acceptable performance in children and working-age adults but no meaningful discrimination between underlying diagnoses in older people (>65 years old).

There were notable differences between individual EEG abnormalities. Features of encephalopathy were common in both psychiatric and medical catatonia, and showed moderate sensitivity and specificity, while features of limbic encephalitis, epileptiform discharges, focal abnormalities and status epilepticus were much less common with low sensitivity but very high specificity.

The strengths of this study included that the performance of the EEG in catatonia was excellent and found consistently across most studies. It is estimated with good precision, model performance and discrimination, so it is unlikely to be due to chance. However, it is quite possible that other findings, such as higher sensitivity than specificity, or subgroup differences, are due to chance given the substantial overlap in confidence intervals.

There are several limitations to this review. Importantly, the included studies were observational, which included case reports and series, typically with a high risk of bias and small sample sizes. Specific issues are selection bias, measurement bias and external validity, which I consider in turn.

Selection bias is likely to have played a role in my findings, as at least four of the 12 larger studies were found to be at high risk of bias for patient selection in the QUADAS-2 and in only 59.8% of the smaller studies did the patient represent the whole experience of the investigator. There is likely to have been reporting bias, as a systematic review found that 20% of catatonia cases had a medical cause, (Oldham, 2018) while in the larger studies 32.1% had a medical cause and in the smaller studies 77.4% had a medical cause. However, this is less of a problem than it may initially seem because there is only limited evidence that reporting bias causes biased results in studies of diagnostic test accuracy (McInnes et al., 2018) and in most of the included studies (particularly the smaller ones), EEGs were only an incidental part of the paper, so it would be unlikely for an EEG finding to substantially influence the decision of whether to publish. There were several studies that reported only psychiatric or only medical cases of catatonia, but a sensitivity analysis excluding these studies did not find that the results were substantially different. Unfortunately, few of the larger studies reported funding, although this is also unlikely to be a major problem in an area where the technology is not protected by intellectual property and where there is little pharmaceutical relevance. The proportion of studies not retrieved was very small (2.8%), so this is unlikely to have substantially affected the results.

In terms of measurement bias, much of the EEG reporting was of poor quality, sometimes denoting EEGs simply as ‘abnormal’ without any indication of which particular abnormalities were present. I was able to partially overcome this by analysing the smaller studies, which tended to give more detailed reports. My results remained robust after excluding cases where psychotropic medications (including benzodiazepines) had been used in the previous 7 days, but it is possible that antiepileptic or anaesthetic drugs also played a role. It is also possible that encephalopathic findings may have been

confused with drowsiness or sleep, as somnolent states may be harder to distinguish clinically in the context of catatonia. Although it is usually possible to distinguish sleep from encephalopathy on the basis of the EEG, (Johnson and Kaplan, 2019) this requires a sufficient length of recording, which was generally not specified in the included reports. One potential problem would be bias towards the null hypothesis if medical causes of catatonia were not adequately identified, resulting in misclassification of medical cases as psychiatric ones. For the larger studies, sensitivity analyses were conducted where studies published before 1980 and those with low concerns about the reference standard were excluded, each finding similar results to the main meta-analysis (Table 38). For the smaller studies, more data were available, so I conducted four sensitivity analyses to try to determine whether there was misclassification, excluding studies prior to 1980, studies prior to 2010, studies with inadequate follow-up time and studies where sufficient investigations were not performed (Table 40). All of these produced similar results. It therefore does not seem likely that misclassification due to inadequate diagnostic investigation explains the results. Among the smaller studies, it was clear in only a minority of cases that alternative causes for catatonia had been adequately ruled out, although a sensitivity analysis excluding such studies was similar to the main analysis. The other issue in terms of measurement bias is that EEGs were often coded by a reporter who already had knowledge of the reference standard, or – conversely – the reference standard was often established by a clinician with prior knowledge of the EEG findings. Some larger studies avoided this, but it is likely to be a problem in any EEG that was requested as part of ordinary clinical care and would inflate the supposed diagnostic test accuracy. However, a sensitivity analysis of the larger studies, excluding those where there may be concerns about the reference standard, found similar results to the main analysis.

In terms of external validity, participants came from a range of psychiatric and medical settings. However, the major concern is that – among those studies where routine clinical records were used – only patients whose clinical presentation apparently justified the use of an EEG were included in the study. It is likely that such patients pose additional diagnostic uncertainty, so it is more reasonable to generalise these results to patients where there is at least some diagnostic uncertainty. If clinicians used the EEG more widely in catatonia, it is likely that more cases of psychiatric catatonia would be included, so the pre-test probability – and thus the positive predictive value – of the EEG would be lower.

The studies also presented considerable heterogeneity in their results. This is particularly apparent in the larger studies. Figure 11 suggests that there may be some negative correlation between sensitivity and specificity, which is the expected outcome where there is a threshold effect in a diagnostic test. (Trikalinos et al., 2012) In a test, such as an EEG, where a report is qualitative, there are often implicit thresholds, above which different studies or clinicians consider the investigation to be abnormal,

(Leeflang et al., 2013) and there is prior evidence that neurophysiologists do exhibit some variability in reporting thresholds. (Jing et al., 2020) This alters the metrics for sensitivity and specificity within an individual study, but the bivariate model used in this meta-analysis takes into account this threshold when producing summary estimates. It does, however, render interpretation more difficult, as it is not clear at what threshold of considering an EEG to be abnormal the summary estimates are taken. Individual EEG abnormalities are probably more straightforward to interpret in this regard, as it is clearer what is being considered abnormal. Another substantial source of heterogeneity was age, which I explored with a subgroup analysis, finding much less support for the utility of the EEG among older adults than in other age groups, which may be due to the increased prevalence of nonspecific slowing in general among older people. (Scally et al., 2018; Woodruff and Kramer, 1979) Moreover, it is possible that additional heterogeneity was introduced by varying definitions, severities and subtypes of catatonia. While a sensitivity analysis of smaller studies restricting to those cases that met DSM-5 criteria for catatonia was similar to the main analysis, it is possible that the EEG findings differ in cases, for example, where catatonia has been defined according to the Northoff Catatonia Scale (Hirjak, Kubera, et al., 2020; Northoff et al., 1999) or catatonia is particularly severe. It might be of particular relevance to understanding any heterogeneity to investigate the EEG findings in malignant catatonia, periodic catatonia or neuroleptic malignant syndrome in future studies.

One particularly interesting finding in the results is that a significant minority of patients with a supposed psychiatric cause for their catatonia had an abnormal EEG, most commonly with features of encephalopathy, which were present in 22 out of 97 (23%) patients in the smaller studies and at least 48 out of 209 (23.0%) patients in the larger studies. A previous review has found that encephalopathic features were the most common EEG abnormalities in catatonia due to a medical condition, but the current study extends this to catatonia due to a psychiatric condition. Since encephalopathy is defined as a pathobiological process in the brain, which distinguishes it from primary psychiatric disorders, this finding is surprising and intriguing. There is a longstanding literature on EEG abnormalities across psychiatric disorders, but the abnormalities described hitherto have not been specific to any diagnostic entity. (Fenton, 1984) I suggest four possible reasons for the generalised slowing in catatonia. Firstly, EEG slowing may reflect an undiagnosed medical condition. There is a substantial overlap between catatonia and delirium, (Ramirez-Bermudez et al., 2022) which has an encephalopathic EEG correlate, and older reports would not have recognised NMDA receptor encephalitis. (Dalmau et al., 2007) Moreover, ictal slowing can occur, (Blumenfeld et al., 2004; Kennedy and Schuele, 2012) although the absence of evidence for epilepsy in most of these case reports means that this is unlikely to be a major explanation. Secondly, EEG abnormalities could reflect various medical complications that have arisen as a result of catatonia, such as sepsis, cardiac

arrhythmia, renal failure, neuroleptic malignant syndrome and hepatic dysfunction. (Funayama et al., 2018) Thirdly, some psychotropic drugs, particularly clozapine, (Jackson and Seneviratne, 2019) have been associated with EEG slowing, although the sensitivity analysis, excluding such cases suggests this is not a major factor. Finally, it is theoretically possible that a mental state itself could lead to EEG abnormalities. Catatonia can certainly generate a marked sympathetic response with fever and tachycardia being common in severe cases (Mann et al., 1986) and even occasionally bilateral dilated pupils unreactive to light. (Agrawal and Das, 2018)

Related to this is the important question of whether the EEG abnormalities I have reported in catatonia represent trait or state, that is, do they represent an enduring latent vulnerability to catatonia, or are they transient phenomena that are closely linked to the clinical presentation? In catatonia secondary to an epileptic seizure, it is to be expected that EEG changes represent a state and are closely linked to the clinical presentation, but even in this scenario the evidence is not straightforward. In a series of three cases of catatonia in the context of status epilepticus, catatonic stupor persisted after electroencephalographic resolution of the seizure, subsequently resolving with either a further benzodiazepine dose or electroconvulsive therapy (ECT). (Suzuki et al., 2006) In a classic study by Gjessing and colleagues, three individuals with periodic catatonia showed an increase in the alpha frequency during phases of stupor. (Gjessing et al., 1967) Several studies have examined cases where generalised slowing was observed during the catatonia. In the study I reported by Smith et al, there were 6 patients who had EEGs during and after catatonia, all of whom showed some improvement, mostly in generalised slowing, but there was not complete normalisation in all patients. (Smith et al., 2012) Other small reports have also described generalised slowing during catatonia (or transition to it) with normal traces before or afterwards. (Ando and Ito, 1959; Annell, 1963) Perhaps most convincingly, in one case report, investigators administered intravenous diazepam during a catatonic state with continuous EEG monitoring, observing marked diminishing of high-amplitude slow activity. (Iseki et al., 2009) It is appears likely, therefore, that generalised slowing on an EEG is a state marker of catatonia, although the data are somewhat preliminary at present.

In conclusion, my results are similar to a previous systematic review of EEG abnormalities in 105 patients with catatonia, which found that the majority of medical catatonia cases had an abnormal EEG, usually generalised slowing. (Carroll et al., 1998) However, my study takes this further by incorporating many more studies and comparing the EEG findings in medical versus psychiatric catatonia cases. Selection and measurement bias are both likely to be present, but sensitivity analyses suggest that they did not have a major effect on my analyses. The fact that an EEG was likely to be used only in cases of diagnostic uncertainty does limit the external validity of my conclusions to such cases. Notwithstanding these limitations, it is reasonable to conclude that the EEG is of value in

discerning whether catatonia has a psychiatric or medical aetiology, but its interpretation relies on the pre-test probability, the specific EEG findings and the results of other investigations.

In terms of the implications for future research, my first suggestion is methodological. EEGs were reported inconsistently and often minimally, lacking important details; there is a need for a minimum reporting standard for EEGs in case reports and series, specifying at a minimum what abnormalities were present, what the patient's state of consciousness was at the time of the recording, what medications had been taken in recent days and who reported the recording. Future studies of the EEG in catatonia should use mixed samples of catatonia secondary to both psychiatric and medical disorders with blinding of reporting staff to the supposed diagnosis; such studies could be conducted retrospectively with existing EEG recordings. Systematic longitudinal follow-up would be important. Given my finding that a large minority of patients have a clear EEG abnormality, catatonia would be an obvious target disorder in studies of quantitative EEG analysis.

The main implication for clinical practice is that the EEG should be considered in cases of catatonia where there is diagnostic uncertainty to support in establishing whether there is a medical or psychiatric underlying disorder. Although it is a safe, non-invasive test, its diagnostic accuracy is such that it should not be used alone but belongs as part of a comprehensive work-up, including history, collateral history, physical examination and other investigations. A normal EEG increases the confidence that catatonia has a psychiatric origin. An abnormal EEG must be interpreted depending on the specific finding: features of encephalopathy have only a moderate specificity, whereas features of limbic encephalitis, epileptiform discharges, focal abnormalities and status epilepticus are highly specific for a medical cause of catatonia. However, caution is required in those aged over 65, where diagnostic accuracy is poor.

7 Conclusions

7.1 Summary

The main findings of this thesis are as follows:

- Aim 1: Neuroimmunology of catatonia. Catatonia is a common feature of NMDAR encephalitis and serum antibodies to the NMDAR may be more common in catatonia than in other severe mental illnesses.
- Aim 2: Epidemiology of catatonia. The incidence of catatonia is approximately 1 per 10,000 person-years and it is overrepresented in individuals from an ethnic minority background. It is associated with an increased duration of hospitalisation but not necessarily with increased mortality.
- Aim 3: Structural neuroimaging findings in catatonia. Structural neuroimaging abnormalities are common on MRI scans of catatonia, but their frequency might not differ from that in other severe mental illnesses.
- Aim 4: EEG findings in catatonia. The EEG is useful in determining the aetiology of catatonia, but it does not perfectly distinguish primary psychiatric disorders from general medical conditions. The most common EEG abnormalities in catatonia are features of encephalopathy.

The major limitations of this work include a partial reliance on very small and likely biased studies and an absence of certain data, such as medications. The use of routinely collected data means that blinding between different sources of information was not performed and selective use of investigations in these patients can create a disease-spectrum bias and impaired external validity.

This thesis concludes that catatonia remains an important problem in clinical and academic neuropsychiatry. However, future studies must be prospective, systematic and with relevant comparison groups. Measures of brain function should be prioritised over imaging of brain structure. However, we should not necessarily anticipate that the pathophysiology of catatonia will be uniform and effective future studies may identify small subsets with a clear biological substrate, which may be genetic or immunological, paving the way for highly targeted trials in specific subpopulations. One of the clearest such groups is NMDAR encephalitis, the evidence for which is now sufficient to suggest that clinicians should at least consider testing in cases of catatonia. This and all other investigations must nevertheless be contextualised in the clinical scenario.

7.2 Main findings

In section 2.9, I presented four aims for this thesis, which were to characterise the neuroimmunology, epidemiology, structural neuroimaging findings and EEG findings in catatonia. I will succinctly present my answers to these issues before considering the main limitations of my responses and some of the implications of the work for future academic and clinical work.

Aim 1: to characterise the neuroimmunology of catatonia. A number of viral, bacterial and parasitic infections have been associated with catatonia, but it is usually not clear whether this is a direct effect of the pathogen or the result of an immunological response. Although activation of the innate immune system can cause withdrawal and psychomotor retardation, it is not certain that it can on its own trigger the full range of catatonic features. Among the plethora of autoimmune disorders associated with catatonia, the overwhelming majority of cases in the literature are of NMDAR encephalitis. Catatonia appears to be a very common feature of NMDAR encephalitis and my data suggest that serum autoantibodies to the NMDA receptor may be more common in catatonia than in other psychiatric inpatients. In terms of other biomarkers, serum iron seems to be lower in catatonia than among psychiatric controls, but – given that CRP and total white cell count were similar to the results in controls – I did not find evidence that low iron is part of a systemic pro-inflammatory state. Creatine kinase was raised, but this may be a downstream effect of catatonia.

Aim 2: to characterise the epidemiology of catatonia. I have been able to use a relatively large dataset to estimate that the incidence of catatonia is approximately 1 per 10,000 person-years. Comparing individuals with catatonia to other patients with severe mental illnesses, those with catatonia had a similar sex ratio but were about 3 years younger on average. Patients with catatonia were substantially more likely to be from an ethnic minority background. Although catatonia seems to be a risk factor for a more prolonged psychiatric admission, it does not appear to be associated with any difference in mortality – at least in the London, UK secondary mental health care services – when other factors, such as age and underlying psychiatric diagnosis are taken into account.

Aim 3: to characterise the structural neuroimaging findings in catatonia. In my findings, which were based on a small proportion of cases (and controls) who underwent MRI scanning for clinical purposes, 34% of scans were judged abnormal by a reporting neuroradiologist. Abnormalities were more commonly bilateral, usually involved the forebrain and the most common pathologies were atrophy, small vessel disease and white matter lesions. However, the findings did not confirm my hypothesis that abnormalities would be more common than in psychiatric inpatients without catatonia: after adjustment for demographic and diagnostic variables, there was no difference from the control group, although the confidence intervals were compatible with a wide range of plausible scenarios.

Aim 4: to characterise the EEG findings in catatonia. In the reported literature, among both medical and psychiatric catatonia, the most common EEG abnormalities were features of encephalopathy. Epileptiform discharges and focal abnormalities also occurred in a minority, while features of limbic encephalitis and status epilepticus were absent in the psychiatric cases and uncommon in the medical cases. An abnormal EEG was 82% (95% CI 67 to 91%) sensitive and 66% (95% CI 45 to 82%) specific for a medical catatonia, but there was still a substantial minority of patients with psychiatric catatonia who had an abnormal EEG.

7.3 Limitations

The above findings have a number of important caveats. These have been considered within the individual chapters, but there are some limitations that have an overall bearing on my conclusions, which I consider here.

Firstly, a recent bibliometric analysis has shown that much of the catatonia literature relies on case reports and small case series. (Weleff et al., 2022) These reports often contain rich detail on the psychopathology and investigations of patients with catatonia, so they were valuable for illustrative purposes in Chapters 3 and 6. It has also been argued that such reports can provide evidence in areas unsuitable for more robust research, they can provide early signals for further investigation and they may be of particular value for rare diseases such as catatonia. (Goldman, 1998; Nissen and Wynn, 2014) However, there are numerous limitations of case reports and series, including recall bias and reporting bias, which may favour rare cases or successful results. (Albrecht et al., 2005; Nissen and Wynn, 2014) Moreover, given that case reports are often selected on the basis of an exposure (e.g. autoimmune encephalitis) and an outcome (e.g. catatonia), they cannot be used to derive incidence or prevalence figures. Although causal inference is challenging with any observational data, in larger studies there is the prospect of using techniques such as adjustment for potential confounders, propensity score matching and negative control groups, but these options are not available when studying case reports. Findings based on case reports should therefore be interpreted with caution, particularly in isolation from other sources of evidence. While the findings in Chapter 6 were largely corroborated by larger observational studies, it is quite possible that some of the conditions noted in Chapter 3 are spurious associations.

Unfortunately, the more recent trend towards research based on large anonymised electronic healthcare records, so called ‘big data’, such as the CRIS system I have used in some of this work, is also not immune from various limitations. Some of these weaknesses may be present simply because the data are not ‘big’ enough: for example, the absence of medication data or the geographical restrictiveness of CRIS could in future be resolved by the addition of prescribing data or expansion to

national systems. However, other weaknesses are not simply resolved by generating more data. These include issues such as data privacy (which is sometimes safeguarded by bureaucratic access systems), high statistical power increasing the risk of type I errors and the risks of post-hoc hypotheses after results are in fact known. (White and Breckenridge, 2014; Zhu et al., 2016) Generating analysis plans prior to manipulating the data were to some degree a safeguard in my work against this latter issue.

Crucially, both case reports and electronic healthcare records rely on routinely collected data as part of clinical care, so they share some limitations. One major weakness that is inherent to both study types is the bias in who is referred for a particular test. Guidelines rightly suggest further investigation for individuals at particular risk of certain medical conditions, so those who undergo a particular test – be that a blood test, MRI scan or EEG – are likely to be unrepresentative of all those with a condition, particularly if only a minority of individuals undergo the relevant investigation. This can create a selection bias if there is differential use of an investigation between two groups under comparison, such as may have occurred in Chapter 5, where factors such as vascular risk factors or index of suspicion for dementia, may have created a bias. Because in Chapter 5 I had data on all those who did not have the relevant investigations, I was able to frame this as a missing data problem and address it with multiple imputation. When writing Chapter 6, however, as a literature review, it was impossible to ascertain the characteristics of the missing data. This issue may also threaten external validity, as it is hard to generalise from a group of patients with catatonia who are highly enriched for an outcome (such as autoimmune encephalitis, as evidenced by the clinician's index of suspicion in requesting neuronal antibody testing) to all patients with catatonia.

Another issue that is embedded into both case reports and larger studies with electronic healthcare records is that of contamination of the interpretation of investigations with a knowledge of the likely clinical diagnosis and vice versa. For instance, knowledge that a patient has mesial temporal lobe atrophy on a structural MRI scan may incline a clinician to label an elderly patient as having Alzheimer's disease rather than considering catatonia. (The two conditions are not necessarily mutually exclusive, (Alisky, 2004; Kendurkar, 2008) but in reality clinicians tend to prioritise diagnoses.) The converse may also be true in that a neurophysiologist reading the EEG of an individual with a known hepatic encephalopathy might interpret some borderline background slowing rather differently compared to that in an individual without such a history. As I argue in section 7.4.7, this is an important and necessary part of good clinical care, but it is problematic for research. This issue was most apparent in Chapter 6, where an ideal study of diagnostic test accuracy would maintain blinding of the index test and the gold standard diagnostic test, as one could consciously or unconsciously influence the other. In reality, given that the majority of studies were in the context of routine clinical care, I suspect that this blinding was broken in most cases. It is also an issue for Chapter 5, where scan interpretation

may have been affected by the indication for a request and the interpretation itself may have influenced the diagnosis. It is perhaps less of an issue in automated laboratory tests, but for autoantibodies there are discrepancies between techniques, laboratories and even between individuals working in the same laboratory, (Mecoli et al., 2020; Ramberger et al., 2015; Suh-Lailam et al., 2016; Yeo et al., 2017) so it is not impossible that such interpretation may be influenced by the clinical scenario. What is much more probable is that the clinical diagnosis is influenced by antibody testing; particularly now that converging pieces of evidence point to a relationship between NMDAR encephalitis and catatonia, it is possible that the diagnosis of the former will prompt the identification of the latter.

7.4 Implications

7.4.1 Catatonia remains an important problem in clinical and academic neuropsychiatry

This thesis has demonstrated that catatonia has not died out or become an insignificant issue. An incidence of 1 per 10,000 person-years places catatonia within the definition of a rare disease, but if we extrapolate to a UK population of 67 million, this would suggest that there are approximately 6700 new cases each year. There was, moreover, no evidence in data from South London that catatonia was becoming any less frequent between 2007 and 2016.

Although catatonia was not associated with an increased mortality in my data, the substantially increased admission duration I found emphasises that catatonia is of prognostic relevance. Recent data specifically from NMDA receptor encephalitis support this finding in that the presence of catatonia was associated with a higher degree of disability, medical complications and ICU admission. (Wu et al., 2023) Catatonia demonstrates the relevance of psychopathology to the practice of psychiatry, as this phenotype does seem to be associated with an increased morbidity.

Moreover, the number and range of case reports of catatonia from all over the world, many of them referenced in this review, demonstrates that cases continue to perplex and challenge clinicians. These reports often contain diagnostic and therapeutic uncertainties that are not readily addressed in the existing literature, highlighting the need for further work in this field.

7.4.2 Future studies of catatonia require relevant comparison groups

A naïve study on structural MRI scans in catatonia might have been conducted in a manner similar to that described in Chapter 5 but without a comparison group. This study might have found that 34% of MRI scans were abnormal in catatonia, which would have been an attention-grabbing headline. It might have made some comparison to normative data, finding that – in contrast – a meta-analysis found that only 2.7% of a healthy population have incidental findings on an MRI scan. (Morris et al.,

2009) The conclusion could have been that brain abnormalities are 12 times more common in catatonia. Previous studies have in fact adopted such an approach, although – in fairness – this has not been the main message of the paper. (Medda et al., 2015; Smith et al., 2012)

While such a result may be eye-catching, it neglects a couple of important issues. The first is that MRI abnormalities are more common in patients with severe mental illnesses than in the general population, (Falkenberg et al., 2017) so the results may not be at all specific to catatonia. The second is that, in routine care, the minority of patients selected for a particular investigation are likely to be highly atypical of the overall population of patients. This was evident in my study in that individuals who had an MRI scan were older than those who did not, but some of the most important patient variables associated with having an MRI scan (e.g. prior neurological disorders, suspicion for dementia, focal neurological signs) were not available.

Chapter 5 provides one example where the addition of a comparison may have fundamentally changed the interpretation of the results, but there are many others. For instance, the CRP of patients with catatonia in Chapter 4 seems rather high (mean 9.1 mg/L), but there is no statistically significant difference from the comparison group, presumably reflecting a non-specific effect in severely unwell psychiatric patients or – as would be expected – the fact that a CRP is preferentially requested when an individual is thought to have some inflammatory process, such as in a suspected acute infection.

The catatonia literature needs to move beyond dramatic uncontrolled studies towards robust epidemiological associations that are demonstrably different from relevant comparison groups. The nature of such comparison groups should vary depending on the research question and the data source. Comparison to healthy controls is often limited because it disregards non-specific associations with psychiatric disorders. However, it may not always be appropriate simply to compare patients with catatonia to an unselected group of patients with psychiatric disorders because there may still be a bias in disease severity: patients with catatonia are often among the most unwell patients in psychiatric services. In Chapters 4 and 5, I compared inpatients with catatonia to other inpatients, essentially matching on a crude measure for disease severity. Another option would be to take a subset of patients with catatonia (e.g. catatonic schizophrenia) and use a disease-matched control group (e.g. non-catatonic schizophrenia). Unfortunately, while these latter two options would be more helpful in determining what abnormalities might be specific to catatonia, in this process they also reduce external validity, as findings are limited to a subset of patients with catatonia. One way to overcome this would be to select a comparison group by matching on, say, underlying diagnosis and treatment setting.

7.4.3 Prospective studies with larger samples of patients with catatonia are necessary

As I mentioned in section 7.3, both case reports and studies using electronic healthcare records have advantages and disadvantages. One limitation that is inherent to them both is that they rely on history, examination and investigation findings that were performed as part of routine clinical care. Where certain assessments have been omitted, data are likely to be missing not at random, so it is not straightforward to estimate what the results might have been.

One way to address this issue in future is with prospective cohort studies, where a standardised battery of clinical assessments is performed alongside investigations such as blood tests, lumbar puncture, EEG and neuroimaging. A comparison group matched for underlying diagnosis could be recruited as well. Given that catatonia is rare and such a study would be resource-intensive, it would make sense to ensure that the data could be used to address multiple hypotheses, so data could be anonymised and made widely available to researchers.

Another option would be to have a national or international case register of patients with catatonia, an approach that was used with neurological and psychiatric presentations of COVID-19. (Varatharaj et al., 2020) This would still rely on clinicians proactively reporting patients, so it would be likely to have more selection bias than a prospective study, but a lower barrier for reporting than formally publishing a case report might mean that the selection bias would be lower than in the existing case report literature. There would also be the issue of missing data for many of the relevant assessments. It would, however, be likely to generate a larger dataset than a prospective cohort study. Outside of the distinctive legal frameworks introduced in the pandemic, there would also be information governance issues to handle carefully.

7.4.4 Catatonia is more likely to be due to brain network dysfunction than to focal neurological lesions

In determining what the underlying pathophysiology of catatonia might be and thus what modalities should be prioritised for future investigation, a comparison of Chapters 5 and 6 is instructive. These addressed the MRI and electroencephalographic findings in catatonia.

In contrast to previous small neuroimaging studies of catatonia, Chapter 5 did not find a particular structural hallmark of catatonia, a finding that has been reinforced by a similar study conducted since mine was published using headache controls. (Magnat et al., 2022) An argument could be made that higher definition scans or computerised analysis may reveal distinctive abnormalities in catatonia. This is indeed possible, but similarly coarse technology without computerised analysis was used in Chapter 6 when studying EEGs and there was an encephalographic signature in at least a subgroup of patients

with catatonia in the form of generalised background slowing. This suggests that measures of brain function may be more illuminating than measures of brain structure.

It is also interesting to look at the actual abnormalities. In both MRI and EEG, findings were predominantly broadly distributed across the brain in the form of generalised atrophy, diffuse white matter lesions and widespread small vessel disease, or generalised background slowing. Focal abnormalities were less common in both MRI and EEG studies and – where they were present in MRI reports – they did not show an overwhelming predilection for one neuroanatomical location. It is more likely that brain abnormalities in catatonia represent interruptions in complex distributed networks than that they locate some single area of the brain.

This conclusion is to some degree supported even by the neuroimmunology findings of this thesis. A systematic review of neuroimaging findings in NMDAR encephalitis, one of the most important neurological disorders associated with catatonia, reported that fewer than half of cases show an abnormal MRI scan. (Bacchi et al., 2018) FDG-PET, a functional imaging modality, sometimes reveals abnormalities in the presence of a normal MRI. (Bacchi et al., 2018)

Given that there is converging evidence for a network dysfunction hypothesis, future neuroimaging research should prioritise functional over structural techniques.

7.4.5 Catatonia has a strong and specific relationship to NMDAR encephalitis

Chapter 3 found that the majority of cases of autoimmune conditions reported in association with catatonia represent NMDAR encephalitis (Table 7). If these were only case reports and case series, this could represent a measurement bias, in which an association is anticipated and therefore looked for in cases. However, the consistent finding of high prevalence of catatonia in cohorts of patients with NMDAR encephalitis (Table 8) implies that this is not a spurious association.

I have been able to add to this finding of a high prevalence of catatonia in NMDAR encephalitis by showing a relatively high prevalence of NMDAR antibodies in the serum of patients with catatonia. Admittedly, the numbers of positive results are small, but this adds to a substantial weight of evidence associating the two conditions.

This evidence has been sufficient to translate the findings to clinical practice with a recommendation in the new British Association for Psychopharmacology guidelines on catatonia that there should be consideration of testing for NMDAR antibodies in serum and CSF of patients experiencing a first episode of catatonia or where the underlying diagnosis is unclear. (Rogers et al., 2023)

7.4.6 The pathophysiology of catatonia may not be uniform and may be exposed in segments

Prior to the discovery of NMDAR encephalitis in 2007, (Dalmau et al., 2007) such cases might have been considered to be seronegative autoimmune encephalitis, presumed viral encephalitis, neuroleptic malignant syndrome or simply malignant catatonia. Further back in history, disorders such as non-convulsive status epilepticus, Wilson's disease or hypothyroidism in catatonia may not have been recognised, leaving a patient with a presumed psychological origin for their catatonia. Historically, I would contend that the greatest advances in understanding catatonia have come not from incremental improvement in seeing catatonia as a whole, but by slicing off small parts of the whole, which have become well understood. In the same vein, the most translational aspect of this thesis may be the use of testing for NMDAR antibodies in clinical practice, which will probably shed no light on the vast majority of cases of catatonia but may be transformative for a small proportion.

Therefore, it is likely to be beneficial to keep subgroups of catatonia in mind in future investigations. Such groups may have a distinctive neuroimmunological or genetic profile, which opens the prospect of novel treatments, as it has done with NMDAR encephalitis.

7.4.7 Investigation of catatonia in clinical practice must be multimodal and interpreted in the light of the clinical scenario

Chapter 5 did not provide convincing evidence for structural neuroimaging as part of a clinical work-up in catatonia, though the evidence for the EEG and neuronal autoantibody testing is more compelling. However, even in cases of positive EEG or antibody findings, the test result alone is not definitive. The area under the ROC curve for an EEG in ascertaining the aetiology of catatonia was 0.83. Meanwhile, there is an emerging literature on misdiagnoses of autoimmune encephalitis, to which overinterpretation of serum antibody results is a major contributor. (Dalmau and Graus, 2023; Flanagan et al., 2023)

The key message is that none of these investigations is on its own diagnostic. I and others have previously suggested that investigations may be overused and rather indiscriminately used, including by psychiatrists, providing a low yield of clinically meaningful results, acting as a poor substitute for history and examination, and generating harm through incidental findings. (Butler et al., 2022; Mathers and Hodgkin, 1989) In catatonia, there are often rational explanations for various investigations, but when they are decontextualised and investigation results are considered to be the only relevant piece of information, they can be deeply misleading. All investigation results in catatonia need to be interpreted in the context of the other information – clinical and paraclinical – about a patient.

7.5 Epilogue

Almost 150 years after Kahlbaum described catatonia, his disorder remains one of the most bizarre and enigmatic in neuropsychiatry. Understanding has advanced, but fundamentally it remains in the liminal space between Griesinger's classification of movement disorders, neither fully psychiatric, nor fully neurological.

Psychological explanations break down when confronted with the extent of the abnormal and purposeless movements (and lack of movement) in catatonia. Moreover, they do not explain abnormal EEG findings that suggest alteration in brain function similar to delirium.

Neurological explanations reach their limits when one considers that no one disorder invariably triggers catatonia. Even NMDAR encephalitis, probably the neurological disorder most robustly linked to catatonia, does not invariably cause catatonia and – when it does – there tends to be fluctuation. This suggests that there are additional factors other than the presence of an antibody that are of relevance in generating the catatonia phenotype. These factors may include genetics, other immunological factors and psychological state.

In this thesis, I have endeavoured to shed some light on this mysterious disorder by drawing together findings from epidemiology, neuroimmunology, neuroimaging and neurophysiology. It highlights that catatonia remains worthy of study but will require the application of modern epidemiological methods, imaging of brain function and a willingness to identify small subpopulations with distinctive pathophysiology.

8 References

Abenson MH (1970) EEGs in Chronic Schizophrenia. *The British Journal of Psychiatry* 116(533). Cambridge University Press: 421–425. DOI: 10.1192/BJP.116.533.421.

Abi-Abib RC, Ramalho, F.V., Conceicao, F.L., et al. (2010) Psychosis as the initial manifestation of pernicious anemia in a type 1 diabetes mellitus patient. *Endocrinologist* 20(5): 224–225. DOI: 10.1097/TEN.0b013e3181f66200.

Abrams R and Taylor MA (1976) Catatonia. *Archives of General Psychiatry* 33(5). American Medical Association: 579. DOI: 10.1001/archpsyc.1976.01770050043006.

Adams AV, Van Mater H, Gallentine W, et al. (2021) Psychiatric Phenotypes of Pediatric Patients With Seropositive Autoimmune Encephalitis. *Hospital pediatrics* 11(7): 743–750. DOI: 10.1542/hpeds.2020-005298.

Agrawal AK and Das S (2018) The catatonic pupil: An unprivileged entity. *Asian Journal of Psychiatry* 32. Elsevier Science B.V.: 75–76. DOI: 10.1016/J.AJP.2017.11.032.

Ahuja N and Carroll B (2007) Possible anti-catatonic effects of minocycline in patients with schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 31(4). Elsevier: 968–969. DOI: 10.1016/J.PNPBP.2007.01.018.

Aiyer R, Novakovic V and Barkin RL (2016) A systematic review on the impact of psychotropic drugs on electroencephalogram waveforms in psychiatry. *Postgraduate Medicine* 128(7). Taylor & Francis: 656–664. DOI: 10.1080/00325481.2016.1218261.

Akanji AO, Ohaeri JU, Al-Shammri S, et al. (2009) Association of blood levels of C-reactive protein with clinical phenotypes in Arab schizophrenic patients. *Psychiatry research* 169(1): 56–61.

Albrecht J, Meves A and Bigby M (2005) Case reports and case series from Lancet had significant impact on medical literature. *Journal of Clinical Epidemiology* 58(12): 1227–1232. DOI: 10.1016/j.jclinepi.2005.04.003.

Al-Diwani AAJ, Pollak TA, Irani SR, et al. (2017) Psychosis: an autoimmune disease? *Immunology* 152(3): 388–401. DOI: 10.1111/imm.12795.

Alisky JM (2004) Is the immobility of advanced dementia a form of lorazepam-responsive catatonia? *American Journal of Alzheimer's Disease and Other Dementias* 19(4): 213–214. DOI: 10.1177/153331750401900404.

American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. Arlington, VA: Amer Psychiatric Pub Incorporated.

Ando M and Ito K (1959) Clinical and electroencephalographical studies on catatonia. *Folia psychiatrica et neurologica japonica* 13(2). Folia Psychiatr Neurol Jpn: 133–142. DOI: 10.1111/J.1440-1819.1959.TB02428.X.

Anglin RE, Rosebush PI and Mazurek MF (2010) Neuroleptic malignant syndrome: a neuroimmunologic hypothesis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 182(18). Canadian Medical Association: E834-8. DOI: 10.1503/cmaj.091442.

Annell AL (1963) Periodic catatonia in a boy of 7 years. *Acta Paedopsychiatrica* 30: 48–58.

Antelmi E, Pizza F, Vandi S, et al. (2017) The spectrum of REM sleep-related episodes in children with type 1 narcolepsy. *Brain* 140(6). Oxford University Press: 1669–1679. DOI: 10.1093/brain/awx096.

Azur MJ, Stuart EA, Frangakis C, et al. (2011) Multiple imputation by chained equations: what is it and how does it work? *International Journal of Methods in Psychiatric Research* 20(1): 40–49. DOI: 10.1002/mpr.329.

Bacchi S, Franke K, Wewegama D, et al. (2018) Magnetic resonance imaging and positron emission tomography in anti-NMDA receptor encephalitis: A systematic review. *Journal of Clinical Neuroscience* 52: 54–59. DOI: 10.1016/j.jocn.2018.03.026.

Bachmann LM, Puhan MA, Riet G ter, et al. (2006) Sample sizes of studies on diagnostic accuracy: literature survey. *BMJ* 332(7550). British Medical Journal Publishing Group: 1127–1129. DOI: 10.1136/bmj.38793.637789.2F.

Bachmann S and Schröder J (2006) Catatonic syndrome related to acute disseminated encephalomyelitis (ADEM). *Schizophrenia Research* 87(1–3): 336–337. DOI: 10.1016/j.schres.2006.04.002.

Balint B, Jarius S, Nagel S, et al. (2014) Progressive encephalomyelitis with rigidity and myoclonus: A new variant with DPPX antibodies. *Neurology* 82(17). Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology: 1521–1528. DOI: 10.1212/WNL.0000000000000372.

Barnes MP, Saunders M, Walls TJ, et al. (1986) The syndrome of Karl Ludwig Kahlbaum. *Journal of Neurology, Neurosurgery & Psychiatry* 49(9). BMJ Publishing Group Ltd: 991–996. DOI: 10.1136/JNNP.49.9.991.

Bauer J and Bien CG (2016) Neuropathology of autoimmune encephalitides. *Handbook of clinical neurology* 133: 107–20. DOI: 10.1016/B978-0-444-63432-0.00007-4.

Bell V, Wilkinson S, Greco M, et al. (2020) What is the functional/organic distinction actually doing in psychiatry and neurology. *Wellcome open research* 5: 138. DOI: 10.12688/wellcomeopenres.16022.1.

Benarous X, Consoli A, Raffin M, et al. (2016) Validation of the Pediatric Catatonia Rating Scale (PCRS). *Schizophrenia Research* 176(2–3). Elsevier: 378–386. DOI: 10.1016/j.schres.2016.06.020.

Berrios GE and Marková IS (2018) Historical and conceptual aspects of motor disorders in the psychoses. *Schizophrenia Research* 200. Elsevier: 5–11. DOI: 10.1016/J.SCHRES.2017.09.008.

Berry N, Sagar R and Tripathi BM (2003) Catatonia and other psychiatric symptoms with vitamin B12 deficiency. *Acta Psychiatrica Scandinavica* 108(2). Munksgaard International Publishers: 156–159. DOI: 10.1034/j.1600-0447.2003.00089.x.

Bharadwaj B, Sugaparaneetharan A and Rajkumar RP (2012) Graves' disease presenting with catatonia: a probable case of encephalopathy associated with autoimmune thyroid disease. *Acta Neuropsychiatrica* 24(06). Cambridge University Press: 374–379. DOI: 10.1111/j.1601-5215.2012.00654.x.

Bini L and Cerletti U (1938) L'elettroshock. *Arch. gen. di neural. Psichiat. e prico anal* 19: 266–268.

Blumenfeld H, Rivera M, McNally KA, et al. (2004) Ictal neocortical slowing in temporal lobe epilepsy. *Neurology* 63(6). Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology: 1015–1021. DOI: 10.1212/01.WNL.0000141086.91077.CD.

Boutros N, Galderisi S, Pogarell O, et al. (2011) EEG in Psychoses, Mood Disorders and Catatonia. In: *Standard Electroencephalography in Clinical Psychiatry*. Wiley, pp. 113–132. DOI: 10.1002/9780470974612.ch8.

Bram D, Bubrovszky M, Durand J-P, et al. (2015) Pernicious anemia presenting as catatonia: correlating vitamin B12 levels and catatonic symptoms. *General Hospital Psychiatry* 37(3): 273.e5-273.e7. DOI: 10.1016/j.genhosppsych.2015.02.003.

Breen J and Hare DJ (2017) The nature and prevalence of catatonic symptoms in young people with autism. *Journal of Intellectual Disability Research* 61(6). John Wiley & Sons, Ltd: 580–593. DOI: 10.1111/jir.12362.

British Paediatric Neurology Association (2021) *Consensus statement on childhood neuropsychiatric presentations, with a focus on PANDAS/PANS*.

Brown S (1997) Excess mortality of schizophrenia: A meta-analysis. *The British Journal of Psychiatry* 171(6). Cambridge University Press: 502–508. DOI: 10.1192/BJP.171.6.502.

Bush G, Fink M, Petrides G, et al. (1996a) Catatonia. I. Rating scale and standardized examination. *Acta Psychiatrica Scandinavica* 93(2): 129–136. DOI: 10.1111/j.1600-0447.1996.tb09814.x.

Bush G, Fink M, Petrides G, et al. (1996b) Catatonia. II. Treatment with lorazepam and electroconvulsive therapy. *Acta Psychiatrica Scandinavica* 93(2): 137–143. DOI: 10.1111/j.1600-0447.1996.tb09815.x.

Butcher NJ, Boot E, Lang AE, et al. (2018) Neuropsychiatric expression and catatonia in 22q11.2 deletion syndrome: An overview and case series. *American Journal of Medical Genetics Part A*. DOI: 10.1002/ajmg.a.38708.

Butler M, Scott F, Stanton B, et al. (2022) Psychiatrists should investigate their patients less. *BJPsych Bulletin* 46(3). Cambridge University Press: 152–156. DOI: 10.1192/bjb.2021.125.

Cai X, Zhou H, Xie Y, et al. (2018) Anti- N -methyl- d -aspartate receptor encephalitis associated with acute Toxoplasma gondii infection. *Medicine (United States)* 97(7): e9924. DOI: 10.1097/MD.0000000000009924.

Caroff SN, Mann SC, Keck PE, et al. (2000) Residual catatonic state following neuroleptic malignant syndrome. *Journal of clinical psychopharmacology* 20(2): 257–9.

Caroff SN, Mann SC, Francis A, et al. (2004) *Catatonia : From Psychopathology to Neurobiology*. American Psychiatric Pub.

Carrol BT and Goforth HW (1995) Serum iron in catatonia. *Biological Psychiatry* 38(11): 776–777. DOI: 10.1016/0006-3223(95)00361-4.

Carroll BT and Boutros NN (1995) Clinical Electroencephalograms in Patients with Catatonic Disorders. *Clinical Electroencephalography* 26(1). SAGE PublicationsSage CA: Los Angeles, CA: 60–64. DOI: 10.1177/155005949502600108.

Carroll BT and Goforth HW (1995) Serum iron in catatonia. *Biological Psychiatry*. DOI: 10.1016/0006-3223(95)00361-4.

Carroll BT and Taylor RE (1981) The Nondichotomy Between Lethal Catatonia and Neuroleptic Malignant Syndrome. *Journal of clinical psychopharmacology.* 17(3): 235–236.

Carroll BT, Anfinson TJ, Kennedy JC, et al. (1994) Catatonic disorder due to general medical conditions. *Journal of Neuropsychiatry and Clinical Neurosciences* 6(2): 122–133. DOI: 10.1176/jnp.6.2.122.

Carroll BT, Goforth HW, Boutros NN, et al. (1998) Electroencephalography in Catatonic Disorders Due to General Medical Conditions and Psychiatric Disorders. *CNS Spectrums* 3(2). Cambridge University Press: 57–61. DOI: 10.1017/S1092852900005551.

Catalano G, Catalano MC, Rosenberg EI, et al. (1998) Catatonia. Another neuropsychiatric presentation of vitamin B12 deficiency? *Psychosomatics* 39(5): 456–60. DOI: 10.1016/S0033-3182(98)71307-6.

Chandrasena R (1986) Catatonic schizophrenia: An international comparative study. *Canadian Journal of Psychiatry* 31(3): 249–252. DOI: 10.1177/070674378603100313.

Chang T, Alexopoulos H, McMenamin M, et al. (2013) Neuronal Surface and Glutamic Acid Decarboxylase Autoantibodies in Nonparaneoplastic Stiff Person Syndrome. *JAMA Neurology* 70(9). American Medical Association: 1140. DOI: 10.1001/jamaneurol.2013.3499.

Chaves C, Castellanos T, Abrams M, et al. (2018) The impact of economic recessions on depression and individual and social well-being: the case of Spain (2006–2013). *Social Psychiatry and Psychiatric Epidemiology* 53(9). Springer: 977–986. DOI: 10.1007/s00127-018-1558-2.

Chen Y-W, Hung P-L, Wu C-K, et al. (2015) Severe complication of catatonia in a young patient with Hashimoto's encephalopathy comorbid with Cornelia de Lange syndrome. *The Kaohsiung journal of medical sciences* 31(1). Elsevier: 60–1. DOI: 10.1016/j.kjms.2014.06.001.

Choi YY, Lee JJ, Choi KY, et al. (2020) The Aging Slopes of Brain Structures Vary by Ethnicity and Sex: Evidence From a Large Magnetic Resonance Imaging Dataset From a Single Scanner of Cognitively Healthy Elderly People in Korea. *Frontiers in Aging Neuroscience* 12. Frontiers: 233. DOI: 10.3389/fnagi.2020.00233.

Chua SE and McKenna PJ (1995) Schizophrenia--a brain disease? A critical review of structural and functional cerebral abnormality in the disorder. *The British journal of psychiatry : the journal of mental science* 166(5). Br J Psychiatry: 563–82. DOI: 10.1192/bjp.166.5.563.

Clinebell K, Azzam PN, Gopalan P, et al. (2014) Guidelines for preventing common medical complications of catatonia: Case report and literature review. *Journal of Clinical Psychiatry* 75(6): 644–651. DOI: 10.4088/JCP.13r08870.

Conca A, Bertsch E, Küng A, et al. (2003) Zuclopenthixol-acetate treatment in catatonic patients: the implication of iron metabolism. *European psychiatry : the journal of the Association of European Psychiatrists* 18(1): 28–31.

Consoli A, Ronen K, An-Gourfinkel I, et al. (2011) Malignant catatonia due to anti-NMDA-receptor encephalitis in a 17-year-old girl: case report. *Child and Adolescent Psychiatry and Mental Health* 5(1). BioMed Central: 15. DOI: 10.1186/1753-2000-5-15.

Corlett PR, Honey GD, Krystal JH, et al. (2011) Glutamatergic Model Psychoses: Prediction Error, Learning and Inference. *Neuropsychopharmacology* 36(1). Nature Publishing Group: 294–315. DOI: 10.1038/npp.2010.163.

Crisp SJ, Balint B and Vincent A (2017) Redefining progressive encephalomyelitis with rigidity and myoclonus after the discovery of antibodies to glycine receptors. *Current Opinion in Neurology* 30(3): 310. DOI: 10.1097/WCO.0000000000000450.

Dale RC, Merheb V, Pillai S, et al. (2012) Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders. *Brain* 135(11): 3453–3468. DOI: 10.1093/brain/aws256.

Dalmau J and Graus F (2018) Antibody-Mediated Encephalitis. *New England Journal of Medicine* 378(9). Massachusetts Medical Society: 840–851. DOI: 10.1056/nejmra1708712.

Dalmau J and Graus F (2023) Autoimmune Encephalitis—Misdiagnosis, Misconceptions, and How to Avoid Them. *JAMA Neurology* 80(1): 12–14. DOI: 10.1001/jamaneurol.2022.4154.

Dalmau J, Tüzün E, Wu H, et al. (2007) Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Annals of neurology* 61(1). NIH Public Access: 25–36. DOI: 10.1002/ana.21050.

Dalmau J, Gleichman AJ, Hughes EG, et al. (2008) Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *The Lancet. Neurology* 7(12). NIH Public Access: 1091–8. DOI: 10.1016/S1474-4422(08)70224-2.

Dalmau J, Lancaster E, Martinez-Hernandez E, et al. (2011) Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *The Lancet. Neurology* 10(1). Elsevier: 63–74. DOI: 10.1016/S1474-4422(10)70253-2.

Daubner SC, Le T and Wang S (2011) Tyrosine Hydroxylase and Regulation of Dopamine Synthesis. *Archives of biochemistry and biophysics* 508(1). NIH Public Access: 1. DOI: 10.1016/J.ABB.2010.12.017.

Dawkins E, Cruden-Smith L, Carter B, et al. (2022) Catatonia Psychopathology and Phenomenology in a Large Dataset. *Frontiers in Psychiatry* 0. Frontiers: 977. DOI: 10.3389/FPSYT.2022.886662.

Deakin B, Suckling J, Barnes TRE, et al. (2018) The benefit of minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BeneMin): a randomised, double-blind, placebo-controlled trial. *The Lancet Psychiatry*. DOI: 10.1016/S2215-0366(18)30345-6.

Dealberto MJ (2008) Catatonia is frequent in black immigrants admitted to Psychiatry in Canada. *International Journal of Psychiatry in Clinical Practice* 12(4): 296–298. DOI: 10.1080/13651500802136402.

Dean DJ, Woodward N, Walther S, et al. (2020) Cognitive motor impairments and brain structure in schizophrenia spectrum disorder patients with a history of catatonia. *Schizophrenia Research* 222. Schizophr Res: 335–341. DOI: 10.1016/j.schres.2020.05.012.

Debette S, Schilling S, Duperron M-G, et al. (2019) Clinical Significance of Magnetic Resonance Imaging Markers of Vascular Brain Injury: A Systematic Review and Meta-analysis. *JAMA*

Neurology 76(1). American Medical Association: 81–94. DOI: 10.1001/JAMANEUROL.2018.3122.

Delvi A, Wilson CA, Jasani I, et al. (2023) Catatonia in the peripartum: A cohort study using electronic health records. *Schizophrenia Research*. DOI: 10.1016/j.schres.2023.02.022.

Denysenko L, Freudenreich O, Philbrick K, et al. (2015) *Catatonia in Medically Ill Patients An Evidence-Based Medicine (EBM) Monograph for Psychosomatic Medicine Practice*. The Guidelines and Evidence-Based Medicine Subcommittee of the Academy of Psychosomatic Medicine (APM); The European Association of Psychosomatic Medicine (EAPM).

Derksen SJ, Goraj B, Molenaar JP, et al. (2013) Severe anti NMDA encephalitis and EBV infection. *Netherlands Journal of Critical Care* 17(5).

Duan B-C, Weng W-C, Lin K-L, et al. (2016) Variations of movement disorders in anti-N-methyl-D-aspartate receptor encephalitis. *Medicine* 95(37): e4365. DOI: 10.1097/MD.0000000000004365.

Dutt A, Grover S, Chakrabarti S, et al. (2011) Phenomenology and treatment of Catatonia: A descriptive study from north India. *Indian journal of psychiatry* 53(1). Indian J Psychiatry: 36–40. DOI: 10.4103/0019-5545.75559.

Dwamena BA (2007) midas: A program for Meta-analytical Integration of Diagnostic Accuracy Studies in Stata. Michigan.

Dwamena BA, Sylvester R and Carlos RC (2007) MIDAS: Stata module for meta-analytical integration of diagnostic test accuracy studies. Available at: https://www.researchgate.net/publication/4922515_MIDAS_Stata_module_for_meta-analytical_integration_of_diagnostic_test_accuracy_studies (accessed 22 June 2022).

Elia J, Dell ML, Friedman DF, et al. (2005) PANDAS With Catatonia: A Case Report. Therapeutic Response to Lorazepam and Plasmapheresis. *Journal of the American Academy of Child & Adolescent Psychiatry* 44(11): 1145–1150. DOI: 10.1097/01.chi.0000179056.54419.5e.

Elias PM (2007) The skin barrier as an innate immune element. *Seminars in Immunopathology* 29(1): 3–14. DOI: 10.1007/s00281-007-0060-9.

Espinola-Nadurille M, Flores-Rivera J, Rivas-Alonso V, et al. (2019) Catatonia in patients with anti-NMDA receptor encephalitis. *Psychiatry and Clinical Neurosciences* 73(9). John Wiley & Sons, Ltd: 574–580. DOI: 10.1111/PCN.12867.

Espinola-Nadurille M, Restrepo-Martínez M, Bayliss L, et al. (2022) Neuropsychiatric phenotypes of anti-NMDAR encephalitis: a prospective study. *Psychological Medicine*: 1–9. DOI: 10.1017/S0033291722001027.

Falkenberg I, Benetti S, Raffin M, et al. (2017) Clinical utility of magnetic resonance imaging in first-episode psychosis. *The British journal of psychiatry : the journal of mental science* 211(4). England: 231–237. DOI: 10.1192/bjp.bp.116.195834.

Fenton GW (1984) The electroencephalogram in psychiatry: clinical and research applications. *Psychiatric developments* 2(1): 53–75.

Fernández Hurst N, Zanetti SR, Báez NS, et al. (2017) Diazepam treatment reduces inflammatory cells and mediators in the central nervous system of rats with experimental autoimmune encephalomyelitis. *Journal of Neuroimmunology* 313. Elsevier: 145–151. DOI: 10.1016/J.JNEUROIM.2017.09.012.

Ferrafiat V, Raffin M, Deiva K, et al. (2017) Catatonia and Autoimmune Conditions in Children and Adolescents: Should We Consider a Therapeutic Challenge? *Journal of Child and Adolescent Psychopharmacology* 27(2). Mary Ann Liebert, Inc. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA : 167–176. DOI: 10.1089/cap.2015.0086.

Fink M (1995) Recognizing NMS as a type of catatonia. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology* 8(1): 75–76.

Fink M and Taylor MA (2006) *Catatonia : A Clinician's Guide to Diagnosis and Treatment.* Cambridge Univ Pr.

Fink M and Taylor MA (2009) The catatonia syndrome: Forgotten but not gone. *Archives of General Psychiatry* 66(11): 1173–1177. DOI: 10.1001/archgenpsychiatry.2009.141.

Flanagan EP, Geschwind MD, Lopez-Chiriboga AS, et al. (2023) Autoimmune Encephalitis Misdiagnosis in Adults. *JAMA Neurology* 80(1): 30–39. DOI: 10.1001/jamaneurol.2022.4251.

Fricchione G and Beach S (2019) Cingulate-basal ganglia-thalamo-cortical aspects of catatonia and implications for treatment. *Handbook of Clinical Neurology* 166. Elsevier: 223–252. DOI: 10.1016/B978-0-444-64196-0.00012-1.

Fritze S, Thieme CE, Kubera KM, et al. (2020) Brainstem alterations contribute to catatonia in schizophrenia spectrum disorders. *Schizophrenia Research* 224. Elsevier: 82–87. DOI: 10.1016/j.schres.2020.09.025.

Funayama M, Takata T, Koreki A, et al. (2018) Catatonic Stupor in Schizophrenic Disorders and Subsequent Medical Complications and Mortality. *Psychosomatic Medicine* 80(4): 370–376. DOI: 10.1097/PSY.0000000000000574.

Fusar-Poli L, Natale A, Amerio A, et al. (2021) Neutrophil-to-lymphocyte, platelet-to-lymphocyte and monocyte-to-lymphocyte ratio in bipolar disorder. *Brain Sciences* 11(1): 1–10. DOI: 10.3390/brainsci11010058.

Gelenberg AJ (1976) The catatonic syndrome. *Lancet (London, England)* 1(7973). Lancet: 1339–41. DOI: 10.1016/s0140-6736(76)92669-6.

Genoud S, Senior AM, Hare DJ, et al. (2019) Meta-analysis of copper and iron in Parkinson's disease brain and biofluids. *Movement Disorders* 35(4): 662–671. DOI: 10.1002/mds.27947.

Gergely P (1999) Drug-Induced Lymphopenia. *Drug Safety* 21(2). Springer: 91–100. DOI: 10.2165/00002018-199921020-00003.

Ghumman UZ, Zaim N, Vidal C, et al. (2022) 3.86 Catatonia in the Child and Adolescent Population at the Johns Hopkins Hospital During the COVID-19 Pandemic: A Retrospective Study. *Journal of the American Academy of Child & Adolescent Psychiatry* 61(10, Supplement). Scientific Proceedings of the 2022 AACAP/CACAP Annual Meeting: S256. DOI: 10.1016/j.jaac.2022.09.364.

Giannoccaro MP, Wright SK and Vincent A (2020) In vivo Mechanisms of Antibody-Mediated Neurological Disorders: Animal Models and Potential Implications. *Frontiers in Neurology* 10. Available at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01394 (accessed 1 May 2023).

Gjessing, Harding, GF, Jenner, FA, et al. (1967) The EEG in three cases of periodic catatonia. *The British journal of psychiatry : the journal of mental science* 113(504): 1271–1282.

Gjessing LR (1964) Studies of periodic catatonia - I. Blood levels of protein-bound iodine and urinary excretion of vanillyl-mandelic acid in relation to clinical course. *Journal of Psychiatric Research* 2(2): 123–134. DOI: 10.1016/0022-3956(64)90007-x.

Gjessing LR (1975) The switch mechanism in periodic catatonia and manic-depressive disorder. *Chronobiologia* 2(4): 307–16.

Gjessing R (1932) Beiträge zur Kenntnis der Pathophysiologie des katatonen Stupors. *Archiv für Psychiatrie und Nervenkrankheiten* 96(1). Springer-Verlag: 319–392. DOI: 10.1007/BF02064336.

Goldman SA (1998) Limitations and strengths of spontaneous reports data. *Clinical Therapeutics* 20: C40–C44. DOI: 10.1016/S0149-2918(98)80007-6.

Gouzoulis-Mayfrank E, Heekeren K, Neukirch A, et al. (2005) Psychological Effects of (S)-Ketamine and N,N-Dimethyltryptamine (DMT): A Double-Blind, Cross-Over Study in Healthy Volunteers. *Pharmacopsychiatry* 38(6): 301–311. DOI: 10.1055/s-2005-916185.

Granata T, Matricardi S, Ragona F, et al. (2018) Pediatric NMDAR encephalitis: A single center observation study with a closer look at movement disorders. *European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society* 22(2): 301–307. DOI: 10.1016/j.ejpn.2018.01.012.

Grover S, Ghosh A and Ghormode D (2014) Do patients of delirium have catatonic features? An exploratory study. *Psychiatry and Clinical Neurosciences* 68(8). Wiley/Blackwell (10.1111): 644–651. DOI: 10.1111/pcn.12168.

Grover S, Chauhan N, Sharma A, et al. (2017) Symptom profile of catatonia in children and adolescents admitted to psychiatry inpatient unit. *Asian Journal of Psychiatry* 29. Elsevier Science B.V.: 91–95. DOI: 10.1016/J.AJP.2017.04.016.

Gruys E, Toussaint MJM, Niewold TA, et al. (2005) Acute phase reaction and acute phase proteins. *Journal of Zhejiang University. Science. B* 6(11). Zhejiang University Press: 1045–56. DOI: 10.1631/jzus.2005.B1045.

Guloksuz S, Rutten BPF, Arts B, et al. (2014) The Immune System and Electroconvulsive Therapy for Depression. *The Journal of ECT* 30(2): 132–137. DOI: 10.1097/YCT.0000000000000127.

Gunne L-M and Gemzell CA (1956) ADRENOCORTICAL AND THYROID FUNCTION IN PERIODIC CATATONIA. *Acta Psychiatrica Scandinavica* 31(4): 367–378. DOI: 10.1111/j.1600-0447.1956.tb09697.x.

Gunning-Dixon FM, Brickman AM, Cheng JC, et al. (2009) Aging of cerebral white matter: a review of MRI findings. *International journal of geriatric psychiatry* 24(2). NIH Public Access: 109–17. DOI: 10.1002/gps.2087.

Hadavi S, Noyce AJ, David Leslie R, et al. (2011) Stiff person syndrome. *Practical Neurology* 11(5). BMJ Publishing Group Ltd: 272–282. DOI: 10.1136/practneurol-2011-000071.

Haouzir S, Lemoine X, Desbordes M, et al. (2009) The role of coagulation marker fibrin D-dimer in early diagnosis of catatonia. *Psychiatry research* 168(1): 78–85. DOI: 10.1016/j.psychres.2008.02.004.

Haroche A, Rogers J, Plaze M, et al. (2020) Brain imaging in catatonia: systematic review and directions for future research. *Psychological Medicine*. Cambridge University Press: 1–13. DOI: 10.1017/S0033291720001853.

Harrison NA, Brydon L, Walker C, et al. (2009) Neural Origins of Human Sickness in Interoceptive Responses to Inflammation. *Biological Psychiatry* 66(5). Elsevier: 415–422. DOI: 10.1016/j.biopsych.2009.03.007.

Harrison NA, Doeller CF, Voon V, et al. (2014) Peripheral inflammation acutely impairs human spatial memory via actions on medial temporal lobe glucose metabolism. *Biological psychiatry* 76(7). Elsevier: 585–93. DOI: 10.1016/j.biopsych.2014.01.005.

Herken and Pruss (2017) Red flags: Clinical signs for identifying autoimmune encephalitis in psychiatric patients. *Frontiers in Psychiatry* 8. (Herken, Pruss) Autoimmune Encephalopathies Group, German Center for Neurodegenerative Diseases (DZNE) Berlin, Berlin, Germany: Frontiers Research Foundation (E-mail: info@frontiersin.org). DOI: 10.3389/fpsyt.2017.00025.

Herrera-Mora P, Munive-Baez L, Ruiz García M, et al. (2021) Anti-N-methyl-D-aspartate receptor encephalitis: An observational and comparative study in Mexican children and adults. *Clinical Neurology and Neurosurgery* 210: 106986. DOI: 10.1016/j.clineuro.2021.106986.

Hill D (1952) EEG in episodic psychotic and psychopathic behaviour. A classification of data. *Electroencephalography and Clinical Neurophysiology* 4(4): 419–442. DOI: 10.1016/0013-4694(52)90074-6.

Hill D (1956) Clinical Applications of EEG in Psychiatry. *Journal of Mental Science* 102(427). Cambridge University Press: 264–271. DOI: 10.1192/BJP.102.427.264.

Hinotsu K, Miyaji C, Yada Y, et al. (2022) The validity of atypical psychosis diagnostic criteria to detect anti-NMDA receptor encephalitis with psychiatric symptoms. *Schizophrenia Research* 248: 292–299. DOI: 10.1016/j.schres.2022.08.024.

Hirjak D, Kubera KM, Wolf RC, et al. (2020) Going Back to Kahlbaum's Psychomotor (and GABAergic) Origins: Is Catatonia More Than Just a Motor and Dopaminergic Syndrome? *Schizophrenia Bulletin* 46(2): 272–285. DOI: 10.1093/schbul/sbz074.

Hirjak D, Rashidi M, Kubera KM, et al. (2020) Multimodal Magnetic Resonance Imaging Data Fusion Reveals Distinct Patterns of Abnormal Brain Structure and Function in Catatonia. *Schizophrenia Bulletin* 46(1). Oxford Academic: 202–210. DOI: 10.1093/schbul/sbz042.

Hosmer DW, Lemeshow S and Sturdivant RX (2013) *Applied Logistic Regression*. Wiley.

Hosseini P, Whincup R, Devan K, et al. (2023) The role of the electroencephalogram (EEG) in determining the aetiology of catatonia: a systematic review and meta-analysis of diagnostic test accuracy. *EClinicalMedicine* 56: 101808. DOI: 10.1016/j.eclinm.2022.101808.

Hozáková L, Slonková J and Blahutová Š (2018) [Anti-NMDAR encephalitis as a serious adverse event probably related to yellow fever vaccination]. *Klinicka mikrobiologie a infekcni lekarstvi* 24(1): 17–19.

Hsu F-G, Sheu M-J, Lin C-L, et al. (2017) Use of Zolpidem and Risk of Acute Pyelonephritis in Women: A Population-Based Case-Control Study in Taiwan. *The Journal of Clinical Pharmacology* 57(3). John Wiley & Sons, Ltd: 376–381. DOI: 10.1002/JCPH.815.

Huang CY, Chou FHC, Huang YS, et al. (2014) The association between zolpidem and infection in patients with sleep disturbance. *Journal of Psychiatric Research* 54(1). Pergamon: 116–120. DOI: 10.1016/J.JPSYCHIRES.2014.03.017.

Hughes EG, Peng X, Gleichman AJ, et al. (2010) Cellular and Synaptic Mechanisms of Anti-NMDA Receptor Encephalitis. *Journal of Neuroscience* 30(17): 5866–5875. DOI: 10.1523/JNEUROSCI.0167-10.2010.

Hutchinson G, Takei N, Sham P, et al. (1999) Factor analysis of symptoms in schizophrenia: differences between White and Caribbean patients in Camberwell. *Psychological Medicine* 29(3). Cambridge University Press: 607–612. DOI: 10.1017/S0033291799008430.

Hutchinson M, Waters P, McHugh J, et al. (2008) Progressive Encephalomyelitis, Rigidity, and Myoclonus: A Novel Glycine Receptor Antibody. *Neurology* 71(16). Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology: 1291–1292. DOI: 10.1212/01.wnl.0000327606.50322.f0.

Inta D, Sartorius A and Gass P (2015) NMDA receptor blockade and catatonia: A complex relationship. *Schizophrenia research* 168(1–2): 581–2. DOI: 10.1016/j.schres.2015.07.029.

Iseki K, Ikeda A, Kihara T, et al. (2009) Impairment of the cortical GABAergic inhibitory system in catatonic stupor: a case report with neuroimaging. *Epileptic Disorders* 11(2): 126–131. DOI: 10.1684/EPD.2009.0257.

Ishibashi T, Sato T, Asano S, et al. (1963) CLINICAL ELECTROENCEPHALOGRAPHIC STUDY OF ATYPICAL ENDOGENOUS PSYCHOSIS. *Psychiatry and Clinical Neurosciences* 16(4). John Wiley & Sons, Ltd: 330–354. DOI: 10.1111/J.1440-1819.1963.TB00675.X.

Iskandar M, Stepanova E and Francis A (2014) Two Cases of Catatonia With Thyroid Dysfunction. *Psychosomatics* 55(6). Elsevier: 703–707. DOI: 10.1016/J.PSYM.2014.01.001.

Jackson A and Seneviratne U (2019) EEG changes in patients on antipsychotic therapy: A systematic review. *Epilepsy & Behavior* 95: 1–9. DOI: 10.1016/j.yebeh.2019.02.005.

Jackson RG, Patel R, Jayatilleke N, et al. (2017) Natural language processing to extract symptoms of severe mental illness from clinical text: The Clinical Record Interactive Search Comprehensive Data Extraction (CRIS-CODE) project. *BMJ Open* 17(7(1)). British Medical Journal Publishing Group: e012012. DOI: 10.1136/bmjopen-2016-012012.

Jaimes-Albornoz W and Serra-Mestres J (2012) Catatonia in the emergency department: Table 1. *Emergency Medicine Journal* 29(11): 863–867. DOI: 10.1136/emermed-2011-200896.

Jauhar S, Blackett A, Srireddy P, et al. (2010) Pernicious anaemia presenting as catatonia without signs of anaemia or macrocytosis. *The British Journal of Psychiatry* 197(3): 244–245. DOI: 10.1192/bjp.bp.108.054072.

Jeyaventhan R, Thanikasalam R, Mehta MA, et al. (2022) Clinical Neuroimaging Findings in Catatonia: Neuroradiological Reports of MRI Scans of Psychiatric Inpatients With and Without Catatonia. *The Journal of Neuropsychiatry and Clinical Neurosciences*. American Psychiatric AssociationWashington, DC. DOI: 10.1176/appi.neuropsych.21070181.

Jézéquel J, Johansson EM, Dupuis JP, et al. (2017) Dynamic disorganization of synaptic NMDA receptors triggered by autoantibodies from psychotic patients. *Nature communications* 8(1): 1791. DOI: 10.1038/s41467-017-01700-3.

Jing J, Herlopian A, Karakis I, et al. (2020) Interrater Reliability of Experts in Identifying Interictal Epileptiform Discharges in Electroencephalograms. *JAMA Neurology* 77(1): 49–57. DOI: 10.1001/jamaneurol.2019.3531.

Johnson EL and Kaplan PW (2019) Clinical neurophysiology of altered states of consciousness: Encephalopathy and coma. *Handbook of Clinical Neurology* 161. Elsevier: 73–88. DOI: 10.1016/B978-0-444-64142-7.00041-2.

Jongsma HE, Gayer-Anderson C, Lasalvia A, et al. (2018) Treated Incidence of Psychotic Disorders in the Multinational EU-GEI Study. *JAMA Psychiatry* 75(1). American Medical Association: 36–46. DOI: 10.1001/JAMAPSYCHIATRY.2017.3554.

Joseph AB, Anderson WH and O'Leary DH (1985) Brainstem and vermis atrophy in catatonia. *The American journal of psychiatry* 142(3). United States: 352–354. DOI: 10.1176/ajp.142.3.352.

Kahlbaum KL (1874) *Die Katatonie : Oder Das Spannungsirresein, Eine Klinische Form Psychischer Krankheit*. Available at: https://archive.org/details/39002079238854.med.yale.edu (accessed 18 August 2017).

Kane N, Acharya J, Beniczky S, et al. (2017) A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017. *Clinical Neurophysiology Practice* 2: 170–185. DOI: 10.1016/j.cnp.2017.07.002.

Keddie S, Pakpoor J, Mousele C, et al. (2020) Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. *Brain*. DOI: 10.1093/brain/awaa433.

Keller U (2019) Nutritional laboratory markers in malnutrition. *Journal of Clinical Medicine* 8(6). Multidisciplinary Digital Publishing Institute (MDPI): 775. DOI: 10.3390/jcm8060775.

Keller WR, Kum LM, Wehring HJ, et al. (2013) A review of anti-inflammatory agents for symptoms of schizophrenia. *Journal of Psychopharmacology* 27(4). SAGE PublicationsSage UK: London, England: 337–342. DOI: 10.1177/0269881112467089.

Kendler KS (2019) The Development of Kraepelin's Mature Diagnostic Concept of Catatonic Dementia Praecox: A Close Reading of Relevant Texts. *Schizophrenia Bulletin*. DOI: 10.1093/schbul/sbz101.

Kendurkar A (2008) Catatonia in an Alzheimer's dementia patient. *Psychogeriatrics* 8(1): 42–44. DOI: 10.1111/j.1479-8301.2007.00218.x.

Kennedy JD and Schuele SU (2012) Neocortical temporal lobe epilepsy. *Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society* 29(5): 366–370. DOI: 10.1097/WNP.0b013e31826bd78b.

Khan A, Joyce P and Jones AV (1980) Benzodiazepine withdrawal syndromes. *The New Zealand medical journal* 92(665): 94–6.

Khan M, Pace L, Truong A, et al. (2016) Catatonia secondary to synthetic cannabinoid use in two patients with no previous psychosis. *The American journal on addictions* 25(1). Am J Addict: 25–7. DOI: 10.1111/ajad.12318.

Kim J and Wessling-Resnick M (2014) Iron and mechanisms of emotional behavior. *Journal of Nutritional Biochemistry* 25(11). NIH Public Access: 1101–1107. DOI: 10.1016/j.jnutbio.2014.07.003.

Kobrynski LJ and Sullivan KE (2007) Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. *The Lancet* 370(9596): 1443–1452. DOI: 10.1016/S0140-6736(07)61601-8.

Koenig M, Camdessanché JP, Duband S, et al. (2005) Myélinolyse extrapontine d'évolution favorable au cours d'une polyendocrinopathie auto-immune. *La Revue de Médecine Interne* 26(1). Elsevier Masson: 65–68. DOI: 10.1016/J.REVMED.2004.09.015.

Kruse JL, Lapid MI, Lennon VA, et al. (2015) Psychiatric Autoimmunity: N-Methyl-D-Aspartate Receptor IgG and Beyond. *Psychosomatics* 56(3): 227–241.

La Vaque TJ (2008) The History of EEG Hans Berger. *http://dx.doi.org.libproxy.ucl.ac.uk/10.1300/J184v03n02_01* 3(2). Taylor & Francis Group: 1–9. DOI: 10.1300/J184V03N02_01.

Lakshmana R, Khanna S and Christopher R (2009) Serum iron levels in Catatonia. *Indian Journal of Psychiatry* 51(s2). (Lakshmana, Khanna, Christopher) Northern Area Mental Health Service, Australia: Medknow Publications and Media Pvt. Ltd: s153.

Lalanne L, Meriot M-E, Ruppert E, et al. (2016) Attempted infanticide and suicide inaugurating catatonia associated with Hashimoto's encephalopathy: a case report. *BMC Psychiatry* 16(1). BioMed Central: 13. DOI: 10.1186/s12888-016-0719-7.

Lancaster E (2016) The Diagnosis and Treatment of Autoimmune Encephalitis. *Journal of clinical neurology (Seoul, Korea)* 12(1). Korean Neurological Association: 1–13. DOI: 10.3988/jcn.2016.12.1.1.

Landis JR and Koch GG (1977) The Measurement of Observer Agreement for Categorical Data. *Biometrics* 33(1): 159. DOI: 10.2307/2529310.

Lee J (1998) Serum iron in catatonia and neuroleptic malignant syndrome. *Biological Psychiatry* 44(6). Elsevier: 499–507. DOI: 10.1016/S0006-3223(98)00109-7.

Lee J, Schwartz D and Hallmayer J (2000) Catatonia in a Psychiatric Intensive Care Facility: Incidence and Response to Benzodiazepines. *Annals of Clinical Psychiatry* 12(2): 89–96. DOI: 10.3109/10401230009147094.

Lee Y and House EM (2017) Treatment of Steroid-Resistant Hashimoto Encephalopathy With Misidentification Delusions and Catatonia. *Psychosomatics* 58(3). Elsevier: 322–327. DOI: 10.1016/J.PSYM.2016.10.008.

Leeflang MMG, Deeks JJ, Takwoingi Y, et al. (2013) Cochrane diagnostic test accuracy reviews. *Systematic reviews* 2(1). BioMed Central: 82. DOI: 10.1186/2046-4053-2-82/FIGURES/1.

Lennox BR, Palmer-Cooper EC, Pollak T, et al. (2017) Prevalence and clinical characteristics of serum neuronal cell surface antibodies in first-episode psychosis: a case-control study. *The lancet. Psychiatry* 4(1). Elsevier: 42–48. DOI: 10.1016/S2215-0366(16)30375-3.

Leon J, Hommer R, Grant P, et al. (2017) Longitudinal outcomes of children with pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS). *European child & adolescent psychiatry*. DOI: 10.1007/s00787-017-1077-9.

Levkovitz Y, Mendlovich S, Riwkes S, et al. (2009) A Double-Blind, Randomized Study of Minocycline for the Treatment of Negative and Cognitive Symptoms in Early-Phase Schizophrenia. *The Journal of Clinical Psychiatry* 70(2). Physicians Postgraduate Press, Inc.: 0–0. DOI: 10.4088/JCP.08M04666YEL.

Lin C-C, Hung Y-Y, Tsai M-C, et al. (2016) Relapses and recurrences of catatonia: 30-case analysis and literature review. *Comprehensive Psychiatry* 66. W.B. Saunders: 157–165. DOI: 10.1016/J.COMPPSYCH.2016.01.011.

Lin C-C, Hung Y-Y, Tsai M-C, et al. (2017) Increased serum anti-N-methyl-D-aspartate receptor antibody immunofluorescence in psychiatric patients with past catatonia. *PLOS ONE* Hashimoto K (ed.) 12(10): e0187156. DOI: 10.1371/journal.pone.0187156.

Liu G, Allen B, Lopez O, et al. (2015) Racial Differences in Gray Matter Integrity by Diffusion Tensor in Black and White Octogenarians. *Current Alzheimer research* 12(7). NIH Public Access: 648–54. DOI: 10.2174/1567205011666141107153634.

Llesuy JR, Coffey MJ, Jacobson KC, et al. (2017) Suspected Delirium Predicts the Thoroughness of Catatonia Evaluation. *The Journal of Neuropsychiatry and Clinical Neurosciences* 29(2). American Psychiatric AssociationArlington, VA: 148–154. DOI: 10.1176/appi.neuropsych.15090230.

Luccarelli J, Kalinich M, McCoy TH, et al. (2022) Co-Occurring Catatonia and COVID-19 Diagnoses Among Hospitalized Individuals in 2020: A National Inpatient Sample Analysis. *Journal of the Academy of Consultation-Liaison Psychiatry*: S2667-2960(22)00629–2. DOI: 10.1016/j.jaclp.2022.12.010.

MacMahon JF and Walter WG (1938) The Electro-Encephalogram in Schizophrenia. *Journal of Mental Science* 84(352). Cambridge University Press: 781–787. DOI: 10.1192/BJP.84.352.781.

Magnat M, Mastellari T, Krystal S, et al. (2022) Feasibility and usefulness of brain imaging in catatonia. *Journal of Psychiatric Research*. DOI: 10.1016/j.jpsychires.2022.11.003.

Mahendra B (1981) Where have all the catatonics gone? *Psychological medicine* 11(4): 669–71.

Mann SC, Caroff SN, Bleier HR, et al. (1986) Lethal catatonia. *American Journal of Psychiatry* 143(11). Am J Psychiatry: 1374–1381. DOI: 10.1176/ajp.143.11.1374.

Markanday A (2015) Acute Phase Reactants in Infections: Evidence-Based Review and a Guide for Clinicians. *Open Forum Infectious Diseases* 2(3). Open Forum Infect Dis. DOI: 10.1093/ofid/ofv098.

Mastellari T, Rogers JP, Cortina-Borja M, et al. (2023) Seasonality of presentation and birth in catatonia. *Schizophrenia Research*. DOI: 10.1016/j.schres.2023.03.015.

Mathers N and Hodgkin P (1989) The Gatekeeper and the Wizard: a fairy tale. *BMJ : British Medical Journal* 298(6667): 172–174.

McCall WV, Shelp FE and McDonald WM (1992) Controlled investigation of the amobarbital interview for catatonic mutism. *The American Journal of Psychiatry* 149(2): 202–206. DOI: 10.1176/ajp.149.2.202.

McCarthy A, Dineen J, McKenna P, et al. (2012) Anti-NMDA receptor encephalitis with associated catatonia during pregnancy. *Journal of Neurology* 259(12): 2632–2635. DOI: 10.1007/s00415-012-6561-z.

McInnes MDF, Moher D, Thombs BD, et al. (2018) Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. *JAMA* 319(4). American Medical Association: 388–396. DOI: 10.1001/JAMA.2017.19163.

Mdege ND, Meader N, Lloyd C, et al. (2017) The Novel Psychoactive Substances in the UK Project: empirical and conceptual review work to produce research recommendations. *Public Health Research* 5(4): 5–45. DOI: 10.3310/PHR05040.

Mecoli CA, Casal-Dominguez M, Pak K, et al. (2020) Myositis Autoantibodies: A Comparison of Results from the Oklahoma Medical Research Foundation Myositis Panel to the Euroimmun Research Line Blot. *Arthritis & rheumatology (Hoboken, N.J.)* 72(1): 192–194. DOI: 10.1002/art.41088.

Medda P, Toni C, Luchini F, et al. (2015) Catatonia in 26 patients with bipolar disorder: clinical features and response to electroconvulsive therapy. *Bipolar Disorders* 17(8). John Wiley & Sons, Ltd: 892–901. DOI: 10.1111/bdi.12348.

Meltzer H (1968) Creatine kinase and aldolase in serum: abnormality common to acute psychoses. *Science (New York, N.Y.)* 159(3821): 1368–1370.

Michael S, Waters P and Irani SR (2020) Stop testing for autoantibodies to the VGKC-complex: only request LGI1 and CASPR2. *Practical Neurology* 20(5). BMJ Publishing Group Ltd: 377–384. DOI: 10.1136/practneurol-2019-002494.

Miyaoka T, Yasukawa R, Yasuda H, et al. (2007) Possible antipsychotic effects of minocycline in patients with schizophrenia. *Progress in neuro-psychopharmacology & biological psychiatry* 31(1): 304–7. DOI: 10.1016/j.pnpbp.2006.08.013.

Morris Z, Whiteley WN, Longstreth WT, et al. (2009) Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. *The BMJ* 339: b3016. DOI: 10.1136/bmj.b3016.

Morrison JR (1974) Changes in subtype diagnosis of schizophrenia: 1920-1966. *American Journal of Psychiatry* 131(6). American Psychiatric Publishing: 674–677. DOI: 10.1176/ajp.131.6.674.

Mueller C, Rufer M, Moergeli H, et al. (2006) Brain imaging in psychiatry - a study of 435 psychiatric in-patients at a university clinic. *Acta psychiatrica Scandinavica* 114(2). Acta Psychiatr Scand: 91–100. DOI: 10.1111/j.1600-0447.2006.00848.x.

Murad MH, Sultan S, Haffar S, et al. (2018) Methodological quality and synthesis of case series and case reports. *BMJ Evidence-Based Medicine* 23(2). Royal Society of Medicine: 60–63. DOI: 10.1136/BMJEBM-2017-110853.

Murphy TK, Patel PD, McGuire JF, et al. (2015) Characterization of the Pediatric Acute-Onset Neuropsychiatric Syndrome Phenotype. *Journal of Child and Adolescent Psychopharmacology* 25(1). Mary Ann Liebert, Inc. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA: 14–25. DOI: 10.1089/cap.2014.0062.

Mustafa M, Bassim RE, Abdel Meguid M, et al. (2012) Ethnic differences in the prevalence of catatonia among hospitalized psychiatric patients in Kuwait. *Middle East Current Psychiatry* 19(4): 214–221. DOI: 10.1097/01.XME.0000418717.09723.3d.

Nagao T and Hirokawa M (2017) Diagnosis and treatment of macrocytic anemias in adults. *Journal of general and family medicine* 18(5). Wiley-Blackwell: 200–204. DOI: 10.1002/jgf2.31.

Nasrallah HA, Schwarzkopf SB, Olson SC, et al. (1990) Gender differences in schizophrenia on MRI brain scans. *Schizophrenia bulletin* 16(2). Schizophr Bull: 205–10. DOI: 10.1093/schbul/16.2.205.

Nievas BGP, Hammerschmidt T, Kummer MP, et al. (2011) Restraint stress increases neuroinflammation independently of amyloid β levels in amyloid precursor protein/PS1 transgenic mice. *Journal of Neurochemistry* 116(1): 43–52. DOI: 10.1111/J.1471-4159.2010.07083.X.

Nikolaus M, Knierim E, Meisel C, et al. (2018) Severe GABA A receptor encephalitis without seizures: A paediatric case successfully treated with early immunomodulation. *European Journal of Paediatric Neurology*. DOI: 10.1016/j.ejpn.2018.01.002.

Nissen T and Wynn R (2014) The clinical case report: a review of its merits and limitations. *BMC Research Notes* 7(1): 264. DOI: 10.1186/1756-0500-7-264.

Niswander GD, Haslerud GM and Mitchell GD (1963) Effect of Catatonia on Schizophrenic Mortality. *Archives of General Psychiatry* 9(6). American Medical Association: 548–551. DOI: 10.1001/archpsyc.1963.01720180020003.

Northoff G (2002) What catatonia can tell us about "top-down modulation": A neuropsychiatric hypothesis. *Behavioral and Brain Sciences* 25(05). Cambridge University Press: 555–577. DOI: 10.1017/S0140525X02000109.

Northoff G, Wenke J and Pflug B (1996) Increase of serum creatine phosphokinase in catatonia: an investigation in 32 acute catatonic patients. *Psychological medicine* 26(3): 547–553.

Northoff G, Koch A, Wenke J, et al. (1999) Catatonia as a psychomotor syndrome: A rating scale and extrapyramidal motor symptoms. *Movement Disorders* 14(3). Wiley-Blackwell: 404–416. DOI: 10.1002/1531-8257(199905)14:3<404::AID-MDS1004>3.0.CO;2-5.

Northoff G, Pfennig A, Krug M, et al. (2000) Delayed onset of late movement-related cortical potentials and abnormal response to lorazepam in catatonia. *Schizophrenia Research* 44(3). Elsevier: 193–211. DOI: 10.1016/S0920-9964(99)00189-9.

Northrop-Clewes CA (2008) Interpreting indicators of iron status during an acute phase response – lessons from malaria and human immunodeficiency virus. *Annals of Clinical Biochemistry* 45(1). SAGE PublicationsSage UK: London, England: 18–32. DOI: 10.1258/acb.2007.007167.

Office for National Statistics (2011) Ethnic group, national identity and religion - Office for National Statistics. *Office for National Statistics*. Available at: https://www.ons.gov.uk/methodology/classificationsandstandards/measuringequality/ethnicgroupnationalidentityandreligion (accessed 17 June 2021).

Office for National Statistics (2022) Estimates of the population for the UK, England, Wales, Scotland and Northern Ireland - Office for National Statistics. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland (accessed 1 March 2023).

Oldham MA (2018) The Probability That Catatonia in the Hospital has a Medical Cause and the Relative Proportions of Its Causes: A Systematic Review. *Psychosomatics* 59(4). Elsevier: 333–340. DOI: 10.1016/j.psym.2018.04.001.

Oruch R, Pryme IF, Engelsen BA, et al. (2017) Neuroleptic malignant syndrome: an easily overlooked neurologic emergency. *Neuropsychiatric disease and treatment* 13. Dove Press: 161–175. DOI: 10.2147/NDT.S118438.

Oxford Diagnostic Immunology service (2015) *Background and aims of NMDA testing guidance document in the Oxford Diagnostic Immunology service*. Oxford University Hospitals NHS Foundation Trust.

Özdin S and Böke Ö (2019) Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. *Psychiatry Research* 271. Elsevier: 131–135. DOI: 10.1016/J.PSYCHRES.2018.11.043.

Papadia S and Hardingham GE (2007) The Dichotomy of NMDA Receptor Signaling. *The Neuroscientist* 13(6). Sage PublicationsSage CA: Los Angeles, CA: 572–579. DOI: 10.1177/1073858407013006040l.

Parsanoglu Z, Balaban OD, Gica S, et al. (2021) Comparison of the Clinical and Treatment Characteristics of Patients Undergoing Electroconvulsive Therapy for Catatonia Indication in the Context of Gender. *Clinical EEG and neuroscience*. SAGE PublicationsSage CA: Los Angeles, CA: 15500594211025888. DOI: 10.1177/15500594211025889.

Pedersen AB, Mikkelsen EM, Cronin-Fenton D, et al. (2017) Missing data and multiple imputation in clinical epidemiological research. *Clinical Epidemiology* 9. Dove Medical Press: 157–166. DOI: 10.2147/CLEP.S129785.

Penninx BW, Milaneschi Y, Lamers F, et al. (2013) Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Medicine* 11(1). BioMed Central: 129. DOI: 10.1186/1741-7015-11-129.

Peralta V, Cuesta MJ, Serrano JF, et al. (1997) The kahlbaum syndrome: A study of its clinical validity, nosological status, and relationship with schizophrenia and mood disorder. *Comprehensive Psychiatry* 38(1). W.B. Saunders: 61–67. DOI: 10.1016/S0010-440X(97)90055-9.

Peralta V, Cuesta MJ, Mata I, et al. (1999) Serum iron in catatonic and noncatatonic psychotic patients. *Biological psychiatry* 45(6): 788–90.

Perry JC and Jacobs D (1982) Overview: clinical applications of the Amytal interview in psychiatric emergency settings. *The American journal of psychiatry* 139(5): 552–559.

Petit-Pedrol M, Armangue T, Peng X, et al. (2014) Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. *The Lancet. Neurology* 13(3): 276–86. DOI: 10.1016/S1474-4422(13)70299-0.

Pettingill P, Kramer HB, Coebergh JA, et al. (2015) Antibodies to GABAA receptor α1 and γ2 subunits: clinical and serologic characterization. *Neurology* 84(12). American Academy of Neurology: 1233–41. DOI: 10.1212/WNL.0000000000001326.

Pfister HW, Preac-Mursic V, Wilske B, et al. (1993) Catatonic syndrome in acute severe encephalitis due to Borrelia burgdorferi infection. *Neurology* 43(2): 433–5.

Philbrick KL and Rummans TA (1994) Malignant catatonia. *The Journal of Neuropsychiatry and Clinical Neurosciences* 6(1): 1–13. DOI: 10.1176/jnp.6.1.1.

Pisetsky DS and Lipsky PE (2020) New insights into the role of antinuclear antibodies in systemic lupus erythematosus. *Nature Reviews Rheumatology* 16(10). 10. Nature Publishing Group: 565–579. DOI: 10.1038/s41584-020-0480-7.

Pollak T, Rogers JP, Nagele RG, et al. (2018) Antibodies in the Diagnosis, Prognosis, and Prediction of Psychotic Disorders. *Schizophrenia Bulletin*. DOI: 10.1093/schbul/sby021.

Pollak T, Iyegbe C, Kempton M, et al. (2018) Neuronal autoantibodies shape symptomatology, cognitive function and brain structure in subjects at ultra-high risk for psychosis. *Neurology, Psychiatry and Brain Research* 29. Elsevier: 19–20. DOI: 10.1016/J.NPBR.2018.01.096.

Powers P, Douglass TS and Waziri R (1976) Hyperpyrexia in catatonic states. *Disease of the Nervous System* 37(6): 359–361.

Prud'homme GJ, Glinka Y and Wang Q (2015) Immunological GABAergic interactions and therapeutic applications in autoimmune diseases. *Autoimmunity Reviews* 14(11). Elsevier: 1048–1056. DOI: 10.1016/J.AUTREV.2015.07.011.

Puentes R, Brenzel A and de Leon J (2017) Pulmonary Embolism during Stuporous Episodes of Catatonia Was Found to Be the Most Frequent Cause of Preventable Death According to a State Mortality Review: 6 Deaths in 15 Years. *Clinical Schizophrenia & Related Psychoses* (aop): CSRP.RPAB.071317. DOI: 10.3371/CSRP.RPAB.071317.

Qin K, Wu W, Huang Y, et al. (2017) Anti-N-methyl-D-aspartate receptor(NMDAR) antibody encephalitis presents in atypical types and coexists with neuromyelitis optica spectrum disorder or neurosyphilis. *BMC neurology* 17(1). BioMed Central: 1. DOI: 10.1186/s12883-016-0787-9.

Raja M, Altavista MC, Cavallari S, et al. (1994) Neuroleptic malignant syndrome and catatonia. *European Archives of Psychiatry and Clinical Neuroscience* 243(6): 299–303.

Ramberger M, Peschl P, Schanda K, et al. (2015) Comparison of Diagnostic Accuracy of Microscopy and Flow Cytometry in Evaluating N-Methyl-D-Aspartate Receptor Antibodies in Serum Using a Live Cell-Based Assay. *PLOS ONE* 10(3). Public Library of Science: e0122037. DOI: 10.1371/journal.pone.0122037.

Ramirez K, Niraula A and Sheridan J (2016) GABAergic modulation with classical benzodiazepines prevent stress-induced neuro-immune dysregulation and behavioral alterations. *Brain, Behavior, and Immunity* 51. Academic Press: 154–168. DOI: 10.1016/J.BBI.2015.08.011.

Ramirez-Bermudez J, Medina-Gutierrez A, Gomez-Cianca H, et al. (2022) Clinical Significance of Delirium With Catatonic Signs in Patients With Neurological Disorders. *https://doi-org.libproxy.ucl.ac.uk/10.1176/appi.neuropsych.18120364* 00. American Psychiatric AssociationWashington, DC: 1–9. DOI: 10.1176/APPI.NEUROPSYCH.18120364.

Rao NP, Mutalik NR, Kasal V, et al. (2011) Monocyte Abnormality in Catatonia: Revisiting the Immune Theory of Catatonia. *The Journal of ECT* 27(3): e53–e54. DOI: 10.1097/YCT.0b013e318212ecaa.

Rasmussen SA, Mazurek MF and Rosebush PI (2016) Catatonia: Our current understanding of its diagnosis, treatment and pathophysiology. *World Journal of Psychiatry* 6(4): 391. DOI: 10.5498/wjp.v6.i4.391.

Rego T and Velakoulis D (2019) Brain imaging in psychiatric disorders: target or screen? *BJPsych open* 5(1). Royal College of Psychiatrists: e4. DOI: 10.1192/bjo.2018.79.

Reid AH, McCall S, Henry JM, et al. (2001) Experimenting on the past: the enigma of von Economo's encephalitis lethargica. *Journal of neuropathology and experimental neurology* 60(7): 663–70.

Reitsma JB, Glas AS, Rutjes AWS, et al. (2005) Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *Journal of Clinical Epidemiology* 58(10): 982–990. DOI: 10.1016/j.jclinepi.2005.02.022.

Richman EE, Skoller NJ, Fokum B, et al. (2018) α-Pyrrolidinopentiophenone ('Flakka') Catalyzing Catatonia: A Case Report and Literature Review. *Journal of addiction medicine* 12(4). J Addict Med: 336–338. DOI: 10.1097/ADM.0000000000000407.

Richter A, Grimm S and Northoff G (2010) Lorazepam modulates orbitofrontal signal changes during emotional processing in catatonia. *Human Psychopharmacology: Clinical and Experimental* 25(1). John Wiley & Sons, Ltd: 55–62. DOI: 10.1002/HUP.1084.

Ripke S, Sanders AR, Kendler KS, et al. (2011) Genome-wide association study identifies five new schizophrenia loci. *Nature Genetics* 43(10). Nature Research: 969–976. DOI: 10.1038/ng.940.

Rogers J (2022) Catatonia: the person's body may be frozen, but their minds are not – new study. Available at: http://theconversation.com/catatonia-the-persons-body-may-be-frozen-but-their-minds-are-not-new-study-182632 (accessed 16 March 2023).

Rogers JP, Pollak TA, Blackman G, et al. (2019) Catatonia and the immune system: a review. *The Lancet Psychiatry* 6(7). Elsevier: 620–630. DOI: 10.1016/S2215-0366(19)30190-7.

Rogers JP, Chesney E, Oliver D, et al. (2020) Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with

comparison to the COVID-19 pandemic. *The Lancet Psychiatry* 7(7). Elsevier: 611–627. DOI: 10.1016/S2215-0366(20)30203-0.

Rogers JP, Pollak TA, Begum N, et al. (2021) Catatonia: Demographic, clinical and laboratory associations. *Psychological Medicine*. Cambridge University Press: 1–11. DOI: 10.1017/S0033291721004402.

Rogers JP, Oldham MA, Fricchione G, et al. (2023) Evidence-based consensus guidelines for the management of catatonia: Recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology (Oxford, England)* 37(4): 327–369. DOI: 10.1177/02698811231158232.

Rosebush P and Stewart T (1989) A prospective analysis of 24 episodes of neuroleptic malignant syndrome. *The American journal of psychiatry* 146(6): 717–25. DOI: 10.1176/ajp.146.6.717.

Rosenblum MD, Remedios KA and Abbas AK (2015) Mechanisms of human autoimmunity. *The Journal of Clinical Investigation* 125(6). American Society for Clinical Investigation: 2228–2233. DOI: 10.1172/JCI78088.

Saha S, Chant D, Welham J, et al. (2005) A systematic review of the prevalence of schizophrenia. *PLoS medicine* 2(5). PLoS Med: e141. DOI: 10.1371/journal.pmed.0020141.

Sahin SK, Yasamali C, Ozyurek MB, et al. (2020) Neutrophil-lymphocyte ratio in catatonia. *Archives of Clinical Psychiatry (São Paulo)* 47(2). Faculdade de Medicina da Universidade de São Paulo: 55–58. DOI: 10.1590/0101-60830000000232.

Saito T, Saito R, Suwa H, et al. (2012) Differences in the Treatment Response to Antithyroid Drugs versus Electroconvulsive Therapy in a Case of Recurrent Catatonia due to Graves' Disease. *Case Reports in Psychiatry* 2012: 1–3. DOI: 10.1155/2012/868490.

Säll L, Salamon E, Allgulander C, et al. (2009) Psychiatric symptoms and disorders in HIV infected mine workers in South Africa. A retrospective descriptive study of acute first admissions. *African journal of psychiatry* 12(3). Afr J Psychiatry (Johannesbg): 206–12. DOI: 10.4314/ajpsy.v12i3.48495.

Scally B, Burke MR, Bunce D, et al. (2018) Resting-state EEG power and connectivity are associated with alpha peak frequency slowing in healthy aging. *Neurobiology of Aging* 71: 149–155. DOI: 10.1016/j.neurobiolaging.2018.07.004.

Scammell TE (2015) Narcolepsy. *New England Journal of Medicine* Campion EW (ed.) 373(27): 2654–2662. DOI: 10.1056/NEJMra1500587.

Schein F, Gagneux-Brunon A, Antoine J-C, et al. (2017) Anti-N-methyl-D-aspartate receptor encephalitis after Herpes simplex virus-associated encephalitis: an emerging disease with diagnosis and therapeutic challenges. *Infection* 45(4): 545–549. DOI: 10.1007/s15010-016-0959-y.

Scheuerecker J, Ufer S, Käpernick M, et al. (2009) Cerebral network deficits in post-acute catatonic schizophrenic patients measured by fMRI. *Journal of psychiatric research* 43(6): 607–14. DOI: 10.1016/j.jpsychires.2008.08.005.

Schulze-Koops H (2004) Lymphopenia and autoimmune diseases. *Arthritis Research & Therapy* 6(4). BioMed Central: 178. DOI: 10.1186/AR1208.

Shlykov MA, Rath S, Badger A, et al. (2016) 'Myxoedema madness' with Capgras syndrome and catatonic features responsive to combination olanzapine and levothyroxine: Table 1. *BMJ Case Reports* 2016: bcr2016215957. DOI: 10.1136/bcr-2016-215957.

Shorter E and Fink M (2018) *The Madness of Fear : A History of Catatonia*. Oxford University Press.

Sienaert P, Rooseleer J and De Fruyt J (2011) Measuring catatonia: A systematic review of rating scales. *Journal of Affective Disorders* 135(1–3): 1–9. DOI: 10.1016/j.jad.2011.02.012.

Sigra S, Hesselmark E and Bejerot S (2018) Treatment of PANDAS and PANS: a systematic review. *Neuroscience & Biobehavioral Reviews* 86: 51–65. DOI: 10.1016/j.neubiorev.2018.01.001.

Singh T and Williams K (2006) Atypical depression. *Psychiatry (Edgmont (Pa. : Township))* 3(4). Matrix Medical Communications: 33–9.

Smith AP, Tyrrell DAJ, Al-Nakib W, et al. (1987) Effects of Experimentally Induced Respiratory Virus Infections and Illness on Psychomotor Performance. *Neuropsychobiology* 18(3): 144–148. DOI: 10.1159/000118408.

Smith JH, Smith VD, Philbrick KL, et al. (2012) Catatonic disorder due to a general medical or psychiatric condition. *Journal of Neuropsychiatry and Clinical Neurosciences* 24(2). American Psychiatric AssociationArlington, VA: 198–207. DOI: 10.1176/appi.neuropsych.11060120.

Snyder S, Prenzlauer S, Maruyama N, et al. (1992) Catatonia in a patient with AIDS-related dementia. *The Journal of clinical psychiatry* 53(11): 414.

Solmi M, Veronese N, Thapa N, et al. (2017) Systematic review and meta-analysis of the efficacy and safety of minocycline in schizophrenia. *CNS Spectrums* 22(05). Cambridge University Press: 415–426. DOI: 10.1017/S1092852916000638.

Solmi M, Pigato GG, Roiter B, et al. (2018) Prevalence of catatonia and its moderators in clinical samples: Results from a meta-analysis and meta-regression analysis. *Schizophrenia Bulletin* 44(5): 1133–1150. DOI: 10.1093/schbul/sbx157.

Spatola M, Petit-Pedrol M, Simabukuro MM, et al. (2017) Investigations in GABA-A receptor antibody-associated encephalitis. *Neurology* 88(11): 1012–1020. DOI: 10.1212/WNL.0000000000003713.

Stauder KH (1934) Die tödliche Katatonie. *Archiv für Psychiatrie und Nervenkrankheiten* 102: 614–634.

Steiner J, Walter M, Glanz W, et al. (2013) Increased Prevalence of Diverse N -Methyl-D-Aspartate Glutamate Receptor Antibodies in Patients With an Initial Diagnosis of Schizophrenia. *JAMA Psychiatry* 70(3): 271. DOI: 10.1001/2013.jamapsychiatry.86.

Stevens JM and Derbyshire AJ (1958) Shifts along the alert-repose continuum during remission of catatonic stupor with amobarbital. *Psychosomatic medicine* 20(2): 99–107. DOI: 10.1097/00006842-195803000-00003.

Stewart R, Soremekun M, Perera G, et al. (2009) The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. *BMC psychiatry* 9. BioMed Central: 51. DOI: 10.1186/1471-244X-9-51.

Stöber G, Franzek E, Haubitz I, et al. (1998) Gender Differences and Age of Onset in the Catatonic Subtypes of Schizophrenia. *Psychopathology* 31(6). Karger Publishers: 307–312. DOI: 10.1159/000029055.

Stompe T, Ortwein-Swoboda G, Ritter K, et al. (2002) Are we witnessing the disappearance of catatonic schizophrenia? *Comprehensive Psychiatry* 43(3). W.B. Saunders: 167–174. DOI: 10.1053/COMP.2002.32352.

Subramaniyam BA, Muliyala KP, Suchandra HH, et al. (2020) Diagnosing catatonia and its dimensions: Cluster analysis and factor solution using the Bush Francis Catatonia Rating Scale (BFCRS). *Asian Journal of Psychiatry* 52: 102002. DOI: 10.1016/j.ajp.2020.102002.

Suh-Lailam BB, Davis KW and Tebo AE (2016) Immunoassays for the detection of IgA antibodies to tissue transglutaminase: significance of multiples of the upper limit of normal and inter-assay correlations. *Clinical Chemistry and Laboratory Medicine (CCLM)* 54(2). De Gruyter: 257–264. DOI: 10.1515/cclm-2015-0348.

Suzuki K, Miura N, Awata S, et al. (2006) Epileptic Seizures Superimposed on Catatonic Stupor. *Epilepsia* 47(4). John Wiley & Sons, Ltd: 793–798. DOI: 10.1111/J.1528-1167.2006.00528.X.

Swedo SE, Leonard HL, Garvey M, et al. (1998) Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *The American journal of psychiatry* 155(2): 264–71. DOI: 10.1176/ajp.155.2.264.

Takács R, Ungvari GS, Antosik-Wójcińska AZ, et al. (2021) Hungarian Psychiatrists' Recognition, Knowledge, and Treatment of Catatonia. *Psychiatric Quarterly* 92(1). Springer: 41–47. DOI: 10.1007/s11126-020-09748-z.

Takwoingi Y, Riley RD and Deeks JJ (2015) Meta-analysis of diagnostic accuracy studies in mental health. *BMJ Ment Health* 18(4). Royal College of Psychiatrists: 103–109. DOI: 10.1136/eb-2015-102228.

Tandon R, Heckers S, Bustillo J, et al. (2013) Catatonia in DSM-5. *Schizophrenia Research* 150(1): 26–30. DOI: 10.1016/j.schres.2013.04.034.

Tang Y, Zou H, Strong JA, et al. (2006) Paradoxical effects of very low dose MK-801. *European Journal of Pharmacology* 537(1–3): 77–84. DOI: 10.1016/j.ejphar.2006.03.016.

Tani A, Kikuta R, Itoh K, et al. (2002) Polymorphism analysis of the upstream region of the human N-methyl-D-aspartate receptor subunit NR1 gene (GRIN1): implications for schizophrenia. *Schizophrenia research* 58(1): 83–6.

Tanskanen A, Taipale H, Cannon M, et al. (2021) Incidence of schizophrenia and influence of prenatal and infant exposure to viral infectious diseases. *Acta Psychiatrica Scandinavica*. John Wiley & Sons, Ltd: acps.13295. DOI: 10.1111/acps.13295.

Taylor D, Gaughran F and Pillinger T (2020) *The Maudsley Practice Guidelines for Physical Health Conditions in Psychiatry*. Wiley.

Taylor MA and Fink M (2003) Catatonia in Psychiatric Classification: A Home of Its Own. *American Journal of Psychiatry* 160(7): 1233–1241. DOI: 10.1176/appi.ajp.160.7.1233.

Tenback DE, van Harten PN and van Os J (2009) Non-therapeutic risk factors for onset of tardive dyskinesia in schizophrenia: A meta-analysis. *Movement Disorders* 24(16). John Wiley & Sons, Ltd: 2309–2315. DOI: 10.1002/mds.22707.

Teplan M (2002) Fundamental of EEG Measurement. *Measurement Science Review* 2(2). Available at: https://www.researchgate.net/publication/228599963_Fundamental_of_EEG_Measurement (accessed 5 July 2022).

Thongprayoon C, Cheungpasitporn W and Kashani K (2016) Serum creatinine level, a surrogate of muscle mass, predicts mortality in critically ill patients. *Journal of Thoracic Disease* 8(5). AME Publishing Company: E305–E311. DOI: 10.21037/jtd.2016.03.62.

Trikalinos TA, Cynthia M. Balion, Craig I. Coleman, et al. (2012) Chapter 8: Meta-Analysis of Test Performance When There Is a "Gold Standard". In: *Methods Guide for Medical Test Reviews*. Agency for Healthcare Research & Quality. Available at: https://effectivehealthcare.ahrq.gov/products/methods-guidance-tests-metaanalysis/methods (accessed 5 July 2022).

Tsutsui K, Kanbayashi T, Tanaka K, et al. (2012) Anti-NMDA-receptor antibody detected in encephalitis, schizophrenia, and narcolepsy with psychotic features. *BMC Psychiatry* 12(1). BioMed Central: 37. DOI: 10.1186/1471-244X-12-37.

Turvey SE and Broide DH (2010) Innate immunity. *Journal of Allergy and Clinical Immunology* 125(2, Supplement 2). 2010 Primer on Allergic and Immunologic Diseases: S24–S32. DOI: 10.1016/j.jaci.2009.07.016.

Unni KE, Shivakumar V, Dutta TK, et al. (1995) Fever of unknown cause presenting as Catatonia. *The Journal of the Association of Physicians of India* 43(2): 134–5.

Urias-Uribe L, Valdez-Solis E, González-Milán C, et al. (2017) Psychosis Crisis Associated with Thyrotoxicosis due to Graves' Disease. *Case Reports in Psychiatry* 2017: 1–4. DOI: 10.1155/2017/6803682.

Ursitti F, Roberto D, Papetti L, et al. (2021) Diagnosis of pediatric anti-NMDAR encephalitis at the onset: A clinical challenge. *European Journal of Paediatric Neurology* 30. W.B. Saunders: 9–16. DOI: 10.1016/J.EJPN.2020.12.004.

van der Heijden FMMA, Tuinier S, Arts NJM, et al. (2005) Catatonia: Disappeared or under-diagnosed? *Psychopathology* 38(1): 3–8. DOI: 10.1159/000083964.

Varatharaj A, Thomas N, Ellul MA, et al. (2020) Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *The Lancet Psychiatry* 7(10). Elsevier: 875–882. DOI: 10.1016/S2215-0366(20)30287-X.

Vasilevska V, Guest PC, Bernstein H-G, et al. (2021) Molecular mimicry of NMDA receptors may contribute to neuropsychiatric symptoms in severe COVID-19 cases. *Journal of Neuroinflammation* 18(1): 245. DOI: 10.1186/s12974-021-02293-x.

von Economo C (1917) Die Encephalitis lethargica. *Wiener klinische Wochenschrift* 30: 581–585.

von Elm E, Altman DG, Egger M, et al. (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. *Annals of Internal Medicine* 147(8). American College of Physicians: 573. DOI: 10.7326/0003-4819-147-8-200710160-00010.

Waisman A, Liblau RS and Becher B (2015) Innate and adaptive immune responses in the CNS. *The Lancet. Neurology* 14(9). Elsevier: 945–55. DOI: 10.1016/S1474-4422(15)00141-6.

Walter WG (1942) Electro-Encephalography in Cases of Mental Disorder. *Journal of Mental Science* 88(370). Cambridge University Press: 110–121. DOI: 10.1192/BJP.88.370.110.

Walther S and Strik W (2016) Catatonia. *CNS Spectrums* 21(04): 341–348. DOI: 10.1017/S1092852916000274.

Walther S, Schäppi L, Federspiel A, et al. (2016) Resting-State Hyperperfusion of the Supplementary Motor Area in Catatonia. *Schizophrenia Bulletin* 43(5). Oxford University Press: sbw140. DOI: 10.1093/schbul/sbw140.

Walther S, Stegmayer K, Federspiel A, et al. (2017) Aberrant Hyperconnectivity in the Motor System at Rest Is Linked to Motor Abnormalities in Schizophrenia Spectrum Disorders. *Schizophrenia Bulletin* 43(5). Oxford Academic: 982–992. DOI: 10.1093/SCHBUL/SBX091.

Warren N, O'Gorman C, McKeon G, et al. (2021) Psychiatric management of anti-NMDAR encephalitis: a cohort analysis. *Psychological Medicine* 51(3). Cambridge University Press: 435–440. DOI: 10.1017/S0033291719003283.

Weleff J, Barnett BS, Park DY, et al. (2022) The State of the Catatonia Literature: Employing Bibliometric Analysis of Articles From 1965–2020 to Identify Current Research Gaps. *Journal of the Academy of Consultation-Liaison Psychiatry*. DOI: 10.1016/j.jaclp.2022.07.002.

Wernicke C (1906) *Grundiss Der Psychiatrie in Klinischen Vorlesungen*. Leipzig: George Thieme.

White P and Breckenridge RS (2014) Trade-Offs, Limitations, and Promises of Big Data in Social Science Research. *Review of Policy Research* 31(4): 331–338. DOI: 10.1111/ropr.12078.

Whiting PF, Rutjes AWS, Westwood ME, et al. (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of internal medicine* 155(8). Ann Intern Med: 529–536. DOI: 10.7326/0003-4819-155-8-201110180-00009.

Wilcox JA (1991) Cerebellar atrophy and catatonia. *Biological Psychiatry*. Netherlands: Elsevier Science. DOI: 10.1016/0006-3223(91)90152-C.

Williams KA, Swedo SE, Farmer CA, et al. (2016) Randomized, Controlled Trial of Intravenous Immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections. *Journal of the American Academy of Child and Adolescent Psychiatry* 55(10): 860-867.e2. DOI: 10.1016/j.jaac.2016.06.017.

Wilson JE, Niu K, Nicolson SE, et al. (2015) The diagnostic criteria and structure of catatonia. *Schizophrenia Research* 164(1–3). Schizophr Res: 256–262. DOI: 10.1016/j.schres.2014.12.036.

Wilson JE, Carlson R, Duggan MC, et al. (2017) Delirium and Catatonia in Critically Ill Patients. *Critical Care Medicine* 45(11): 1837–1844. DOI: 10.1097/CCM.0000000000002642.

Wohleb ES, Franklin T, Iwata M, et al. (2016) Integrating neuroimmune systems in the neurobiology of depression. *Nature Reviews Neuroscience* 17(8). Nature Research: 497–511. DOI: 10.1038/nrn.2016.69.

Woodruff DS and Kramer DA (1979) Eeg alpha slowing, refractory period, and reaction time in aging. *Experimental Aging Research* 5(4). Routledge: 279–292. DOI: 10.1080/03610737908257205.

Workman JL and Nelson RJ (2011) Potential animal models of seasonal affective disorder. *Neuroscience & Biobehavioral Reviews* 35(3). Pergamon: 669–679. DOI: 10.1016/J.NEUBIOREV.2010.08.005.

World Health Organization (1973) *Report of the International Pilot Study of Schizophrenia*. WHO offset publication ; no. 2. Geneva, Switzerland: World Health Organization. Available at: https://apps.who.int/iris/handle/10665/39405.

World Health Organization (1992) *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization.

World Health Organization (2018) *International Classification of Diseases for Mortality and Morbidity Statistics (11th Revision)*. Available at: https://icd.who.int/browse11/l-m/en.

Wu H, Wu C, Zhou Y, et al. (2023) Catatonia in adult anti-NMDAR encephalitis: an observational cohort study. *BMC Psychiatry* 23(1): 94. DOI: 10.1186/s12888-022-04505-x.

Wu J, Zou H, Strong JA, et al. (2005) Bimodal effects of MK-801 on locomotion and stereotypy in C57BL/6 mice. *Psychopharmacology* 177(3): 256–63. DOI: 10.1007/s00213-004-1944-1.

Yeo T, Chen Z, Chai JYH, et al. (2017) Detection of LGI1 and CASPR2 antibodies with a commercial cell-based assay in patients with very high VGKC-complex antibody levels. *Journal of the Neurological Sciences* 378: 85–90. DOI: 10.1016/j.jns.2017.04.045.

Yeoh SY, Roberts E, Scott F, et al. (2022) Catatonic Episodes Related to Substance Use: A Cross-Sectional Study Using Electronic Healthcare Records. *Journal of Dual Diagnosis*. Routledge. DOI: 10.1080/15504263.2021.2016342.

Zaman H, Gibson RC and Walcott G (2019) Benzodiazepines for catatonia in people with schizophrenia or other serious mental illnesses. *The Cochrane database of systematic reviews* 8(8). Cochrane Database Syst Rev: CD006570. DOI: 10.1002/14651858.CD006570.pub3.

Zhou F-C, Lee JWY, Zhang Q-H, et al. (2020) Higher Serum C-Reactive Protein Levels in Catatonic Patients: A Comparison to Non-catatonic Patients and Healthy Controls. *Schizophrenia Bulletin* 46(5). Oxford Academic: 1155–1164. DOI: 10.1093/schbul/sbaa041.

Zhu VZ, Tuggle CT and Au AF (2016) Promise and Limitations of Big Data Research in Plastic Surgery. *Annals of Plastic Surgery* 76(4): 453. DOI: 10.1097/SAP.0000000000000750.

Zingela Z, Stroud L, Cronje J, et al. (2022) Management and outcomes of catatonia: A prospective study in urban South Africa: *https://doi.org/10.1177/20503121221105579* 10. SAGE PublicationsSage UK: London, England: 205031212211055. DOI: 10.1177/20503121221105579.

Zucca FA, Segura-Aguilar J, Ferrari E, et al. (2017) Interactions of iron, dopamine and neuromelanin pathways in brain aging and Parkinson's disease. *Progress in Neurobiology* 155. Pergamon: 96–119. DOI: 10.1016/J.PNEUROBIO.2015.09.012.

Zulfic Z, Weickert CS, Weickert TW, et al. (2020) Neutrophil-lymphocyte ratio - a simple, accessible measure of inflammation, morbidity and prognosis in psychiatric disorders? *Australasian psychiatry : bulletin of Royal Australian and New Zealand College of Psychiatrists* 28(4). SAGE PublicationsSage UK: London, England: 454–458. DOI: 10.1177/1039856220908172.