

Journal Pre-proof

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PII: S0022-3956(22)00627-6

DOI: <https://doi.org/10.1016/j.jpsychires.2022.11.003>

Reference: PIAT 5426

To appear in: *Journal of Psychiatric Research*

Received Date: 30 June 2022

Revised Date: 25 October 2022

Accepted Date: 12 November 2022

Please cite this article as: Magnat M, Mastellari T, Krystal S, Hanafi R, Mateos M, Hacein-Bey L, Haroche A, Rogers JP, Williams SR, Pruvo JP, Amad A, Feasibility and usefulness of brain imaging in catatonia, *Journal of Psychiatric Research* (2022), doi: <https://doi.org/10.1016/j.jpsychires.2022.11.003>.

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Feasibility and usefulness of brain imaging in catatonia

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Abstract

Catatonia is a well characterized psychomotor syndrome that has recognizable motor, affective, behavioural and vegetative manifestations. Despite recent demonstration that catatonia is often associated with brain imaging abnormalities, there is currently no consensus or guidelines about the role of brain imaging. In this study, we assessed the feasibility of brain imaging in a series of patients with catatonia in a routine clinical setting and estimated the prevalence of clinically relevant radiological abnormalities.

Sixty patients with catatonia were evaluated against sixty non-healthy controls subjects with headache. The MRI reports were reviewed, and MRI scans were also interpreted by neuroradiologists using a standardised MRI assessment.

In this cohort, more than 85% of brain scans of patients with catatonia revealed abnormalities. The most frequently reported abnormalities in the catatonic group were white matter abnormalities (n = 44), followed by brain atrophy (n = 27). There was no evidence for significant differences in the frequency of abnormalities found in radiology reports and standardised neuroradiological assessments. The frequency of abnormalities was similar to that found in a population of non-healthy controls subjects with headache.

This study shows that MRI is feasible in patients with catatonia and that brain imaging abnormalities are common findings in these patients. Most frequently, white matter abnormalities and diffuse brain atrophy are observed.

Keywords: MRI, brain imaging, catatonia, neuroimaging

Introduction

Catatonia is a well characterized psychomotor syndrome that has recognizable motor, affective, behavioural and vegetative manifestations. Initially considered as a subtype of schizophrenia for decades since its first description (Fink et al., 2010), catatonia is now categorised either as a specifier of a mental disorder when it presents as an isolated manifestation, or as an associated element when present along with another medical condition, in about 20-25% of cases (e.g. viral infections, encephalitis, drugs withdrawal, autoimmune diseases) (Tandon et al., 2013). Catatonia is common in clinical samples (mean prevalence 9.0%) (Solmi et al., 2018), and may be complicated by a broad range of conditions, including venous thromboembolism, dehydration, pressure ulcers, acute renal failure and cardiac arrest, some of these being life-threatening (Funayama et al., 2018).

Although the diagnosis of catatonia is primarily a clinical one, further testing can be considered depending on the clinical circumstances such as blood tests, EEG and lumbar puncture (if there are signs of encephalitis or meningitis) (Daniels, 2009). Currently, the role of brain imaging remains unclear. Despite a recent systematic review finding that catatonia is often associated with brain imaging abnormalities (in more than 75% of 137 brain imaging case reports) (Haroche et al., 2020), there is no consensus or guidelines about the role of brain imaging in catatonia in clinical practice. Surprisingly, to the best of our knowledge, no studies have been conducted so far investigating the feasibility and usefulness of brain imaging in clinical practice, for patients diagnosed with catatonia, in a prospective and standardised manner.

The aim of the present study is to assess the feasibility of brain imaging in a series of patients with catatonia in clinical practice, and to estimate the prevalence of clinically relevant abnormalities on structural MRI in this cohort.

Materials and methods

Participants and study design

Between November 2015 and August 2020, a total of sixty patients were sequentially included in this cohort. Inclusion criteria were 1) a diagnosis of catatonia made by senior psychiatrists according to DSM-5 criteria (American Psychiatric Association, 2013) and 2) the presence of structural Magnetic Resonance Imaging (MRI) brain scans, obtained as part of the standardised investigation for patients with catatonia. Exclusion criteria were absolute and relative contraindications to MRI (i.e., implantable devices, metallic bodies, drug infusion pumps, inferior vena cava filters, surgical clips).

All patients were admitted for full-time hospitalisation at Fontan Hospital (the psychiatry ward of Lille University Medical Centre, Lille, France) and received a standardised, complete evaluation of the catatonic state by medical staff. Demographic and clinical data such as age, sex, medical history and psychiatric diagnosis according to the DSM-5 were collected for all participants. A full physical examination as well as blood tests were performed. Structural MR images were obtained for each patient, to exclude abnormalities potentially linked to other conditions and as an evaluation before potential electroconvulsive therapy (ECT).

This observational, non-interventional study using routinely collected data, received approval from the *Commission Nationale de l'Informatique et des Libertés* (CNIL) and the Local Data Protection Service (DEC19-076). This study was designed as a case-control study, comparing patients suffering from catatonia, with non-healthy controls.

The control group consisted of subjects suffering from headache, receiving an MRI scan at the Rothschild Foundation, Paris, France, as part of the standard neurological evaluation.

Patients from the control group did not have any history of psychiatric disorder, nor of catatonia. Catatonic patients and controls were matched by age and sex.

Image acquisition and Radiological assessment

All MRI scans were performed and interpreted by consultant neuroradiologists. Findings referring to features outside the skull which did not involve brain tissue (i.e., abnormalities of the skulls, sinuses, face or skin) were not considered in the study. Full brain and skull coverage was a requirement.

Regarding the patients with catatonia, MRI scans were obtained using the Philips Achieva 3.0T scanner (Philips, Best, The Netherlands) at Lille University Hospital, and included 3-dimensional T1-weighted gradient echo (3D T1) and two-dimensional fluid-attenuated inversion recovery (2D FLAIR). 3D T1 sequence was acquired with 283 slices, 1 mm slice thickness, a 26 × 24 x 17 cm field of view, TR = 7,1 ms, TE = 3,2 ms, flip angle 9 degrees. 2D FLAIR was acquired with 32 slices, 4mm slice thickness, a 23 × 18 x 14 cm field of view, inversion time (TI) = 2800 ms, TR = 11000 ms, TE = 125 ms, flip angle 90 degrees.

Regarding the control group, 3D T1- weighted sequences were obtained using the Philips Elition 3.0T scanner (Philips, Best, The Netherlands) at Rothschild Hospital (Paris, France). This sequence was acquired with 324 slices, 0.9 mm slice thickness, a 28 × 24 x 18 cm field of view, TR = 7,1 ms, TE = 3,2 ms, flip angle 9 degrees. 3D-FLAIR was also acquired. This sequence was optimised by lengthening its TR to 8000 ms, modifying its TI value to allow satisfactory fluid suppression, increasing its turbo factor and setting its effective TE to be as short as possible. The details of the used parameters are available here (Lecler et al., 2019).

Standardised neuroradiological assessment

MRI scans were interpreted by three neuroradiologists (M.M., R.H., S.K.), who used a standardised system for MRI assessment consisting of the following:

- White matter lesions were quantified according to the Fazekas scale, an internationally used reference score based on the size and number of lesions (Fazekas et al., 1987).
- Brain atrophy was defined by a semi quantitative rating scale, as 0 (no atrophy), 1 (mild to moderate atrophy) or 2 (severe atrophy).
- Medial temporal lobe atrophy was quantified using Scheltens' scale, which scores from 0 to 4 based on the width of the choroid fissure, the width of the temporal horn of the lateral ventricle and the height of the hippocampus (Scheltens et al., 1995).
- Dilated Virchow-Robin spaces were defined using a semi-quantitative scale, as 0 (no dilated spaces), 1 (non-pathological, slightly dilated spaces), 2 (mildly dilated spaces, in commonly affected brain areas), 3 (severe dilatation and/or dilated spaces in unusual brain areas)
- Microbleeds were quantified using a quantitative scale, as 0 (no microbleeds observed), 1 (fewer than 5 microbleeds), 2 (between five and 10 microbleeds), 3 (more than 10 microbleeds)

A third of scans were first reviewed by all three neuroradiologists, for the purposes of ascertaining inter-rater agreement. Since established scoring systems were used, which all neuroradiologists had significant experience and familiarity with, the initial phase of the review process was considered equivalent to the establishment of excellent inter-rater agreement, thereby obviating the need for Cohen kappa statistics. Therefore, the remainder of MRI scans were subsequently assessed separately by all three neuroradiologists. Interpretation of MRI scans was not blind to cases and controls.

Radiology reports

MRI reports were initially reviewed by two trained and experienced raters (M.M. and T.M.) and categorised as normal or abnormal. In cases of disagreement, a third investigator (A.A.) arbitrated. Abnormalities were subsequently categorised according to the nature of lesions (e.g. cortical or subcortical, leukoencephalopathy, diffuse brain atrophy), lateralisation in the brain, and severity (Katzman et al., 1999).

Statistical analysis

Differences in the frequency of clinically relevant abnormalities between 1) radiology reports versus standardised neuroradiological assessment and 2) between catatonic patients and controls were tested by means of a chi-squared or McNemar test. Statistical analyses were performed using JAMOVİ (2.0) in the R statistical language (<https://www.jamovi.org>).

Results

Study subjects

Sixty patients with catatonia were included in this study and evaluated against sixty controls. All patients were able to undergo brain MRI. Table 1 summarises demographic and disease-related data of the study subjects. One radiology report and 3 MRI scan could not be included in the analysis because they were not found in the patient's record. Examples of brain MRI abnormalities in catatonic patients are provided in Figure 1.

MRI findings

Overall, 88% (n = 52) the brain scans from the catatonic group revealed imaging abnormalities. The most frequently reported abnormalities in the catatonic group were white matter abnormalities (n = 44, 75%), followed by brain atrophy (n = 27, 46%).

Comparison between radiology reports and standardised neuroradiological reports

Table 2 summarises the nature and frequency of abnormalities found by radiologists (radiology reports) versus those noted using standardized neuroradiological assessments. There was no evidence for significant differences in the frequency of abnormalities between radiology reports and standardised neuroradiological assessments.

Frequency of abnormalities & comparison between catatonic patients versus controls

Table 2 summarises the frequency of brain imaging abnormalities and shows a comparison between patients with catatonia and controls. There was no evidence for significant differences in the frequency of abnormalities between patients with catatonia versus controls.

Discussion

The aim of this study was to assess the feasibility of brain imaging in patients diagnosed with catatonia and to estimate the frequency of brain imaging abnormalities in our sample of patients with catatonia, using two different methods for interpreting MRI scans and comparing with a control group of patients suffering from unspecified headaches.

All patients included in our study were able to successfully undergo MRI scans, including those who were agitated, demonstrating therefore the feasibility of brain imaging in patients with catatonia. Stereotypy, agitation, negativism, impulsivity, and combativeness are some of the catatonic signs that may prevent radiologists from completing a full MRI procedure, which can be a long and potentially stressful technique. When performing MRI scans in patients with catatonia, the major issue is to manage agitation. Despite high doses of lorazepam that are used as the main treatment of the catatonic syndrome, agitation can persist, so an alternative premedication, such as clonidine, can be considered (Gagnon et al., 2017; Zhang et al., 2013). Therefore, brain imaging in catatonia seems to be a feasible option and could be easily implemented in further studies.

The presence of neuroimaging abnormalities in patients with catatonia has previously been described in case reports and several case series (Haroche et al., 2020). Another recent study has recently examined abnormalities in neuroimaging reports in 79 patients with catatonia, compared to a psychiatric control group (Jeyaventhana et al., 2022), but this study did not have a standardised neuroradiological reporting tool and relied on clinical reports, which may be biased by indication and radiologist. To our knowledge, our study is the first to evaluate a large cohort of patients with catatonia against a control group (non-psychiatric patients without catatonia, suffering from headaches) using a standardized neuroradiological reporting tool.

Women were over-represented in our study ($n = 40$, 66%), and Haroche et al., 2020 found similar results (57%) (Haroche et al., 2020). Although Medda et al., 2015 have suggested an over-representation of women among catatonic patients (88.5%) (Medda et al., 2015), other studies have shown otherwise, so the issue of a sex difference remains inconclusive (Espinola-Nadurille et al., 2016; Solmi et al., 2018). The different proportions of women being diagnosed with catatonia could be related to the underlying aetiology of the syndrome. Catatonia is often associated with mood disorders and autoimmune diseases, which are known to be more prevalent among women (Ferrari et al., 2013; Ngo et al., 2014).

Despite attempts at standardization (Kahn et al., 2009), radiology reports are left with significant variability, largely reflecting the personal biases of radiologists. Such differences in style, although not a major determinant of quality, rely on subjective assessments (Scott and Palmer, 2015). The purpose of the comparison between routine radiology reports and standardised neuroradiological assessments was to study if there were significant differences in detecting brain abnormalities, between a simple reading of the radiology report by a psychiatrist, and a standardised interpretation of scans by a radiologist. Our results showed no significant differences in terms of frequency of the abnormalities observed between the two methods. Indeed, our results suggest that routine radiology reports are reliable descriptions of brain imaging abnormalities in patients with catatonia. For now, brain imaging in catatonic patients seems not to require a specific standardised interpretation of images, nor a specific training for specialised neuroradiologists.

This study estimated the frequency of clinically relevant pathology on MRI scans of patients with catatonia and controls. 7 scans were normal in the catatonic group (20%) and 4 were normal in control group (7%). However, when we compared the scans between the groups with and without catatonia, we found no differences in the proportion of scans with an abnormality.

These results may be due to the comparison of catatonic patients with a pathological control group, suffering from unspecified headaches, instead of healthy subjects. However, we believe that this does not impact significantly the validity of our study. Our two groups seem to be comparable in terms of frequency of brain imaging abnormalities. It is important to bear in mind that catatonia can be associated with both primary psychiatric conditions and several diseases touching the CNS, such as infectious, autoimmune and neurodegenerative processes. Patients from our control group did not have any medical history of catatonic syndrome.

Thirty-nine percent ($n = 23$, 39%) of patients with catatonia had evidence on imaging of WMH. WMH are known to increase with age and to be associated with age-related risk factors, such as cardiovascular disease, smoking, diabetes, hypertension and hyperlipidaemia (Zhuang et al., 2018). WMH are also known to have a high prevalence among individuals with psychiatric disorders in general (Beyer et al., 2009), including depression (Wang et al., 2014) and schizophrenia (Keshavan et al., 1996).

Forty-six percent ($n = 27$, 46%) of our patients with catatonia showed diffuse brain atrophy, which was not significantly different in comparison with the control group (39%). This is in line with several studies that have revealed diffuse cerebral and cerebellar atrophy in patients with catatonia (Haroche et al., 2020; Jeyaventhana et al., 2022). Table 2 shows that brain imaging abnormalities are common findings in patients with catatonia. Indeed, similar findings were highlighted by Haroche et al., 2020, who described brain imaging abnormalities in catatonia in more than 75% of cases, where the most frequent were diffuse lesions of white matter and diffuse cerebral atrophy. Altogether, currently available studies provide with a body of evidence that catatonia is associated with dysfunction of brain networks, rather than being the product of damage to isolated brain regions (Daniels, 2009).

Despite the similar brain abnormalities between patients with catatonia and controls suffering from headaches, brain imaging still represents an essential step in the clinical assessment of catatonic patients, to exclude neurological and inflammatory conditions that might be the primary cause of catatonia. In terms of neuroscientific research, functional brain imaging might provide further interesting insights on the link between catatonia and brain abnormalities.

One of the main limitations of our study is the relatively small sample size, although it is larger than almost all other studies of catatonia neuroimaging. Another important limitation is the use of patients suffering from headaches as controls, rather than healthy subjects. In fact, a control group consisting of healthy subjects not suffering from any neurological or psychiatric disorder was unavailable for this study. Although this represents a serious limitation for the case-control analyses, our findings still show a substantial percentage of brain abnormalities in patients suffering from catatonia in daily clinical practice. Furthermore, the interpretation of imaging scans conducted by the neuroradiologists was standardised, but not blind to the diagnosis of catatonia or headache. Moreover, it can be difficult to distinguish if brain imaging abnormalities are due to the catatonic syndrome itself, or the underlying cause. Future studies should try to control for this bias, comparing patients with catatonia with other patients suffering from the same underlying disease, but without any catatonic signs. Finally, one of the strengths of the present study is the naturalistic and prospective design, which is the closest possible to routine clinical practice. In fact, structural MRI scans were requested in the context of a standardised clinical and instrumental evaluation of catatonia.

In conclusion, our study shows that MRI is feasible in patients with catatonia and that brain imaging abnormalities are common findings in these patients. Most frequently, WMH and diffuse brain atrophy are observed. These abnormalities seem to be as frequent as those of patients suffering from headaches, matched for age and sex. We still do not know what the clinical

meaning of these abnormalities is. Further studies are needed to explore the relevance and importance of these findings in the clinical practice. To date, little is known about the pathophysiology and aetiopathogenesis of catatonia, despite growing studies on the subject during the last few years. We believe that future neuroimaging research on larger numbers of patients with catatonia would be highly useful, focusing both on structural and functional abnormalities, using quantitative volume measurements and neural network assessments. It is worth underlying that neuroimaging techniques in psychiatry are still considered as fundamental research tools, rather than necessary explorations in clinical practice. In fact, scans are mostly used to exclude non-psychiatric underlying lesions, and still cannot drive diagnostic or therapeutic algorithms in routine psychiatry. However, machine-learning and computational approaches using Artificial Intelligence (AI) seem to be promising strategies for precision psychiatry in the near future, helping clinicians predicting the clinical response and disease outcomes (de Pierrefeu et al., 2018; Nielsen et al., 2020). We therefore suggest that brain imaging may represent an important tool towards better comprehension and treatment of catatonia. Future studies may use AI techniques and machine learning algorithms to try predicting clinical response to benzodiazepines and/or ECT, decreasing the risk of malignant catatonia and favouring better treatment outcomes.

Conflict of interests

The authors declare no conflict of interest. SW is supported in part by the Medical Research Council Centre for Neurodevelopmental Disorders, King's College London (MR/N026063/1), Wellcome Trust/EPSRC Centre for Medical Engineering and the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre (BRC).

Tables and Figure captions

Table 1. Demographic and disease-related characteristics of catatonic patients and controls

Table 2. Frequency of abnormalities and comparison between 1) radiology reports and standardised neuroradiological assessment and 2) Standardised assessments (catatonia)vs standardised assessments (controls)

Figure 1. Examples of brain MRI abnormalities in catatonic patients, a) T1 weighted image shows central and cortical atrophy, prominent perivascular spaces b) significant periventricular white matter FLAIR hyperintensities, c) periventricular FLAIR hyperintense foci and right medial parietal cortical ischemic lesion, d) FLAIR hyperintense basal ganglia lesions

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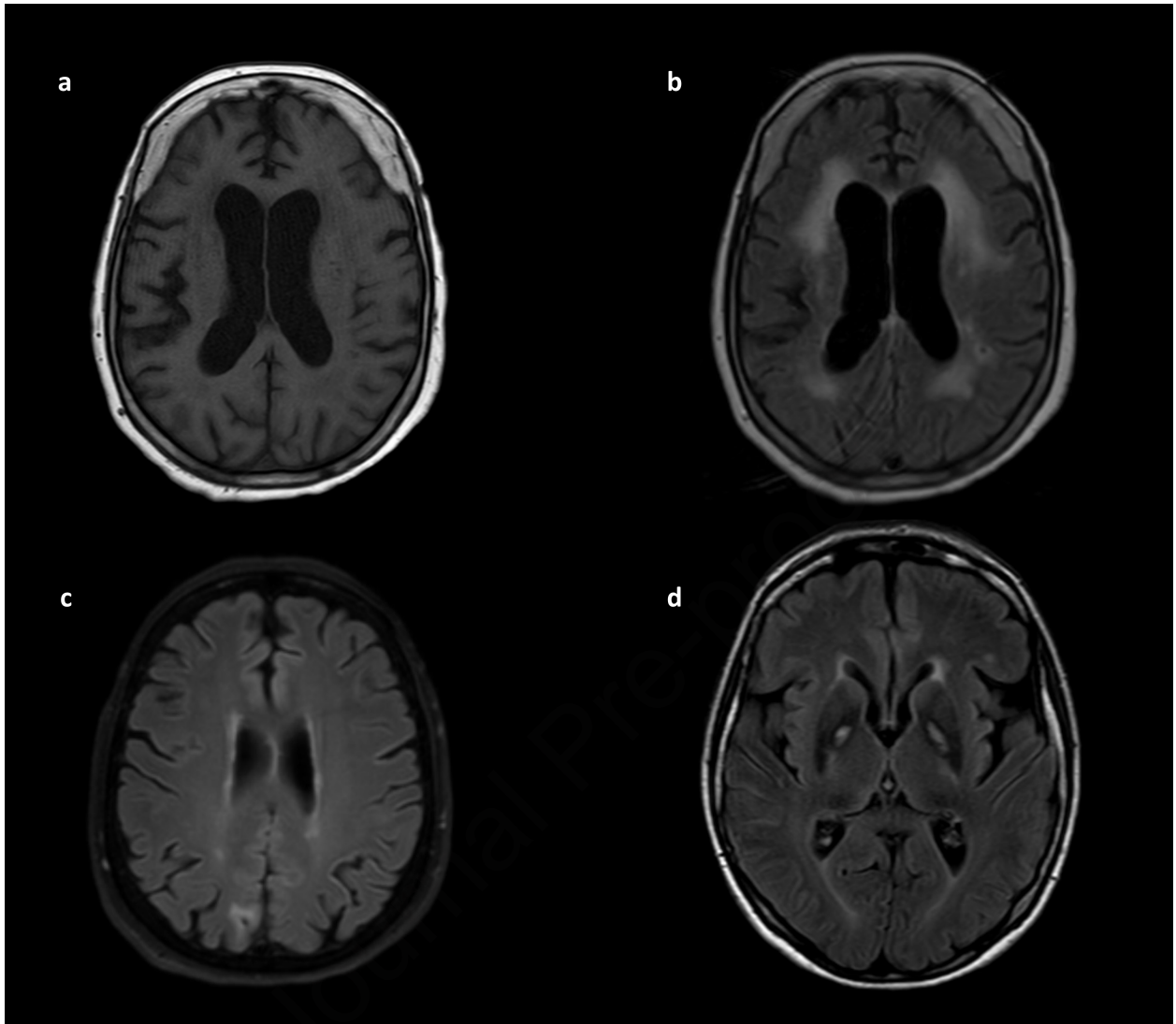
	Patients with catatonia (N = 60)	Controls (N = 60)
Age, years	Mean (SD) 60 (18.9)	Mean (SD) 53.5 (18.4)
Sex	N (%)	N (%)
- Female	40 (66)	40 (66)
- Male	20 (34)	20 (34)
Primary psychiatric diagnosis	N (%)	
- Major Depressive Disorder (%)	18 (30)	
- Bipolar disorder (%)	11 (18)	
- Schizophrenia and schizoaffective disorder (%)	10 (17)	
- Non-psychiatric cause (encephalitis, auto-immune disease) (%)	11 (18)	
- Dementia	4 (7)	
- Neuroleptic malignant syndrome	3 (5)	
- Unknown	3 (5)	

Table 1. Demographic and disease-related characteristics of catatonic patients and controls

	Radiology reports (catatonia) vs standardised assessments (catatonia)				Standardised assessments (catatonia) vs standardised assessments (controls)		
	Abnormalities found in radiology reports in catatonic patients N (%) N total = 59	Abnormalities found by using standardised neuroradiological assessment in catatonic patients N (%) N total = 57	X ²	P-value	Abnormalities found by using standardised neuroradiological assessment in patients with headaches N (%) N total = 60	X ²	P-value
Any abnormality	52 (88.1)	52 (91.2)	0.30	0.59	56 (93.3)	0.18	0.67
White matter abnormalities	44 (74.6)	44 (77.2)	0.11	0.74	45 (75)	0.077	0.78
White Matter Hyperintensities (WMH) (Fazekas scale)							
0	36 (61.0)	34 (59.6)			30 (50)		
1	12 (20.3)	12 (21.1)			15 (25)		
2	7 (11.9)	7 (12.3)	0.02	1.00	13 (21.7)	2.98	0.40
3	4 (6.8)	4 (7.0)			2 (3.3)		
Brain atrophy							
0	32 (54.2)	30 (52.6)			37 (61.7)		
1	22 (37.3)	22 (38.6)	0.03	0.99	20 (33.3)	1.25	0.54
2	5 (8.5)	5 (8.8)			3 (5.0)		
Fronto-temporal atrophy	3 (5.1)	3 (5.3)	0.00	0.97	1 (1.7)	1.15	0.29
Parieto-occipital atrophy	6 (10.2)	6 (10.5)	0.00	0.95	7 (11.7)	0.04	0.84
Medial temporal lobe atrophy	0 (0)	0 (0)	-	-	1 (1.7)	0.96	0.33
Scheltens' scale							
0	38 (65.5)	29 (59.2)			29 (48.3)		
1	9 (15.5)	9 (18.4)			15 (25)		
2	9 (15.5)	9 (18.4)	0.46	0.93	14 (23.3)	1.49	0.68
3	2 (3.4)	2 (4.1)			2 (3.3)		
Dilated Virchow-Robin spaces							
0	24 (40.7)	22 (38.6)			29 (48.3)		
1	30 (50.8)	30 (52.6)			27 (45)		
2	4 (6.8)	4 (7.0)	0.05	1.00	4 (6.7)	2.04	0.56
3	1 (1.7)	1 (1.8)			0 (0)		
Post-ischemic lesions	2 (3.4)	2 (3.5)	0.00	0.97	2 (3.3)	0.00	0.96
Microbleeds							
0	48 (82.8)	45 (81.8)			49 (81.7)		
1	9 (15.5)	9 (16.4)	0.02	0.99	9 (15)	0.29	0.87
2	1 (1.7)	1 (1.8)			2 (3.3)		
Deep microbleeds							
1 (<5)	6 (10.3)	6 (10.9)			7 (11.7)		
2 (5-10)	0 (0)	0 (0)	0.01	0.92	0 (0)	0.02	0.90
3 (>10)	0 (0)	0 (0)			0 (0)		
Superficial microbleeds							
1 (<5)	3 (5.2)	3 (5.5)			2 (3.3)		
2 (5-10)	1 (1.7)	1 (1.8)	0.01	1.00	2 (3.3)	0.55	0.76
3 (>10)	0 (0)	0 (0)			0 (0)		
Infratentorial microbleeds							
1 (<5)	7 (12.1)	7 (12.7)	0.01	0.92	4 (6.7)	1.22	0.27

	2 (5 -10)	0 (0)	0 (0)		0 (0)		
	3 (> 10)	0 (0)	0 (0)		0 (0)		
Hemosiderosis		1 (1.7)	1 (1.8)	0.00	0.97	2 (3.3)	0.26 0.61
Post-haemorrhagic lesions		1 (1.7)	0 (0)	0.96	0.33	1 (1.7)	0.93 0.34
Developmental venous anomaly		4 (6.9)	4 (7.3)	0.01	0.94	3 (5)	0.26 0.61
Cavernoma		2 (3.5)	2 (3.7)	0.00	0.96	3 (5)	1.21 0.55
Arteriovenous malformation		0 (0)	0 (0)	-	-	0 (0)	- 1.00
Aneurysm		2 (3.5)	2 (6.1)	0.32	0.57	4 (6.7)	0.01 0.91
Arachnoid cysts		2 (3.4)	2 (3.5)	0.00	0.97	1 (1.7)	3.07 0.38
Pineal cysts		3 (5.1)	3 (5.3)	0.00	0.97	3 (5)	0.00 0.95
Basal ganglia abnormalities		5 (8.5)	5 (8.8)	0.00	0.96	3 (5)	0.65 0.42

Table 2. Frequency of abnormalities and comparison between 1) radiology reports and standardised neuroradiological assessment and 2) Standardised assessments (catatonia)vs standardised assessments (controls)



Conflict of interests

The authors declare no conflict of interest. SW is supported, in part by the Medical Research Council Centre for Neurodevelopmental Disorders, King's College London (MR/N026063/1), Wellcome Trust/EPSRC Centre for Medical Engineering and the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre (BRC).

Journal Pre-proof

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