Clinical neuroimaging findings in catatonia: neuroradiological reports of MRI scans compared to psychiatric inpatients without catatonia

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Abstract

Objective

Catatonia is a debilitating psychomotor disorder. Previous neuroimaging studies have used small samples with inconsistent results. We aimed to describe the structural neuroradiological abnormalities in clinical MRI brain scans of patients with catatonia and compare them to psychiatric inpatients without catatonia. We report the largest study of catatonia neuroimaging to date.

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, Black ethnicity and psychiatric diagnosis.

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 comparison group. Radiological abnormalities were reported in 27 out of 79 cases (34.2%) and in 338 out of 711 in the comparison 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%).

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.

Introduction

Catatonia is a psychomotor syndrome characterised by a state of reduced responsiveness and inability to move normally despite complete physical capacity.{1} It is recognised to occur in a variety of mental disorders and reportedly affects 5-18% of patients with acute severe psychiatric illness.{2} It may also occur in the context of many neurological and general medical disorders. {3} It is a serious and debilitating condition, associated with multiple life-threatening complications, yet it is often underdiagnosed.{4}

Previously classified as a subtype of schizophrenia and organic mental disorders, the 11th revision of the International Classification of Diseases and Related Health Problems (ICD-11) now recognises catatonia as a distinct neuropsychiatric syndrome and DSM-5 permits a diagnosis of catatonia in the context of any psychiatric or general medical disorder.{5; 6} Despite diverse aetiologies, the generally positive response to benzodiazepines regardless of the underlying cause provides some evidence for a unified disorder.{7} Nonetheless, its pathophysiology has remained elusive: theories about the neurotransmitters GABA, dopamine and glutamate as well as hypotheses regarding phenomenology, neural networks and neuroinflammation remain unconfirmed. {8–13}

Findings from neuroimaging studies in catatonia have been inconsistent. Focal lesions associated with catatonia have been identified in sites as diverse as the frontal lobes, parietal lobes, temporal lobes, basal ganglia, anterior cingulate gyrus, thalamus, pons and cerebellum.{14} A recent systematic review reported that most cases had diffuse and focal white matter lesions, occurring in many different regions.{15} Furthermore, functional imaging frequently showed frontal, temporal or basal ganglia hypoperfusion, while structural imaging mostly showed diffuse cerebral atrophy.{15} However, most brain imaging studies in catatonia are case reports or series describing findings in a small sample of patients. While these studies are of interest, the samples are not large enough to identify patterns, they are prone to selection bias and have often lacked comparison groups. To date, no studies have explored the structural neuroimaging findings in a large population of patients with catatonia with an appropriate comparison group.

Here we present a study which utilised a large dataset to describe neuroimaging findings in clinical MRI reports, comparing them to psychiatric patients without catatonia. Our specific objectives were (1) among patients with catatonia to identify the distribution of abnormalities in terms of laterality, localisation and pathology, and (2) to compare the frequency of such MRI abnormalities in psychiatric patients with and without catatonia.

Methods

Study design

This study was a case-control study comparing the neuroradiological abnormalities in clinical reports of MRI brain scans of patients with catatonia to psychiatric patients without catatonia. Anonymised electronic healthcare records from patients seen in the South London and Maudsley NHS Foundation Trust, London, UK were accessed through the Clinical Records Interactive Search (CRIS). The CRIS system has previously been described {16} and is approved by the Oxfordshire C Research Ethics Committee (ref. 18/SC/0372); this specific study was approved by the CRIS Oversight Committee (ref. 17-102).

Outcome

Cases of catatonia were defined as having a clinician diagnosis of catatonia and at least two features on the Bush-Francis Catatonia Screening Instrument, a reliable and validated instrument for the

detection of catatonia, {7; 17; 18} as described in previous work by this group.{19} As this was a heterogeneous population with a range of different diagnoses, the comparison group comprised all patients admitted to psychiatric wards in the Trust who had never had a catatonia diagnosis. All patients with catatonia in the final analysis had also been psychiatric inpatients.

Exposure

The exposure 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 electronic healthcare records and MRI clinical radiological reports were extracted, where available, from the electronic records for all patients selected as above admitted to a hospital ward. The following data were extracted from structured fields in the records: age at index date, sex, ethnicity, involuntary detention within two weeks following the index date, and primary ICD-10 diagnosis. The index date for patients with catatonia was the date of the first identified catatonic episode; for the comparison group, the date of hospital admission was used as the index date. When a diagnosis had been made prior to the index date, the most recent diagnosis prior to the index date was used; when this was not available, the earliest diagnosis up to six months after the index date was used. MRI scans were reported by consultant neuroradiologists, of whom there are currently eight. Scans that occurred at any time before the index date or within 90 days after the index date were included. Scans obtained more than 90 days after the index date were excluded on pragmatic grounds, as there was a higher risk that they included abnormalities that had developed after the index illness. Where there were multiple scans available for one patient, the scan that was nearest to the index date was used. The procedure is illustrated in Figure 1.

All available MRI reports from 2008 to 2018 were compiled in a spreadsheet. The reports were categorised and numerically coded for the presence of abnormalities by their anatomical location, pathological description, and lateralisation. In scans with multiple abnormalities, each abnormality was coded separately by these criteria to minimise loss of data. Extracranial abnormalities were excluded. All reports were evaluated independently by two investigators (RJ and RT) who were blinded to the diagnostic groups and each other's assessments. Where there was disagreement, a third investigator (JPR) arbitrated. The study size was determined pragmatically based on the number of available cases.

Following data collection, small cell sizes were merged based on *a priori* relationships between categories blind to group membership. The anatomical areas were merged based on embryological brain structure and the pathologies were merged according to the main underlying mechanism.

Confounders

The potential confounders considered were age on date of scan, sex (male/female), Black ethnicity and diagnostic group. We chose to adjust for these potential confounders because they have previously been associated with differences in brain MRI findings {20–24} and have been associated with risk of catatonia in prior studies.{25–28} Ethnicity categories were grouped according to the preferred categories of the UK Office for National Statistics; {29} Mixed / Multiple ethnic groups were combined with Other ethnic group to avoid small cell sizes. Primary diagnoses were 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).

Statistical analysis

We 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, and ethnicity.

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

We 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, we used Fisher's exact test, as there were numerous small cell sizes.

Missing data were assumed to be missing at random. Therefore, to explore the impact of missing data on our estimates, as a sensitivity analysis, we imputed missing exposure data for participants with complete outcome data using multiple imputation by chained equations. We imputed 20 datasets 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 were abnormal scan, catatonia, age at scan, sex, Black ethnicity, diagnostic group, electroconvulsive therapy use within two weeks after index, age at index (either onset of catatonia or hospital admission), date of birth, date of scan, diastolic blood pressure, systolic blood pressure, date of death, time from referral to index date, time from index date to documentation, end date of catatonic episode, Health of the Nation Outcome Scale (HoNOS) score, HoNOS date, index date, duration of admission, MMSE score, episode order, death within follow-up, involuntary detention and validity of MRI report. The observed and imputed data are compared in Supplementary Table 1. The analysis used Stata MP version 15.1.

The manuscript is written according to the STROBE guidelines {30} and the STROBE checklist can be found in Supplementary Table 2.

Results

Participants

Out of 1,456 patients with catatonia and 24,956 patients in the comparison 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 comparison group (2.8% of all patients in the comparison group), as illustrated in Figure 1. 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.

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%). Patients of Black ethnicity appeared more likely to have an MRI scan, but the groups were similar in terms of age and sex (Supplementary Table 3).

Demographic and disease-related characteristics

Table 1 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 comparison group. Handedness of subjects is not available in this dataset.

Abnormalities

In total, 365 out of 790 scans (46.2%) were reported as abnormal. As shown in Table 2, 34.2% of the catatonia group had an abnormal scan, compared to 47.5% of the comparison 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, Black 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 Supplementary Table 4.

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 comparison 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, Black ethnicity and diagnostic group, the OR was 0.96 (95% CI 0.75 to 1.23), p=0.74.

Lateralisation

Table 3 shows that most abnormal scans had at least one bilateral abnormality in both the catatonia and comparison groups. We found no evidence of difference in lateralisation of abnormalities between the groups (p = 0.98).

Anatomical Location

Abnormalities were reported across various brain regions, as shown in Table 3. The majority of abnormalities were in the forebrain in both groups. We 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).

Pathology

The numbers of scans reporting different categories of pathology are reported in Table 3. 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).

Discussion

Neuroimaging abnormalities in patients with catatonia have previously been described in case reports and other studies with small sample sizes, often without a comparison 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, we 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 we compared the scans between the groups with and without catatonia, we found no differences in the proportion of scans reported to have an abnormality after adjustment for age, sex, Black ethnicity and diagnostic group. Secondary analyses also found no evidence for a difference in the number of abnormalities, lateralisation, anatomical location or pathology.

To our knowledge, this is the largest study of catatonia neuroimaging published to date. {15} It also has the advantage of representing patients with catatonia across a range of underlying disorders and it has an appropriate comparison 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 our 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 comparison group, so this would potentially lead to a selection bias. The characteristics of the comparison group have been shown to have a substantial effect on outcomes in studies of neuroimaging in psychiatric patients. {31} 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 organic diagnoses are more likely to be referred for neuroimaging. {32; 33}

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 our sensitivity analysis using multiple imputation is likely to provide a more accurate 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), {32} so it is likely that it is not a wholly adequate method of dealing with the missing data.

In terms of confounding, we were able to adjust our 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. described 26 patients with catatonia resistant to benzodiazepines, finding that the CT or MRI scan was abnormal in 17 (65%, 95% CI 44 – 83%).{34} Smith et al. examined the MRI scans of 31 patients with catatonia, finding

abnormalities in at least 18 (58%, 95% CI 39 – 75%).{35} It is possible that our 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.{34–36} 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.{15} Taken together, our 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.{10} 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.{37}

However, when we examine 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 our knowledge, no prior studies have 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,{36} while the other focussed solely on cerebellar atrophy.{38} This emphasises the high rate of brain abnormalities in patients with psychiatric disorders, especially schizophrenia and other neuropsychiatric conditions severe enough to require admission, and the need for a psychiatric comparison group in studies of catatonia. Previous work with data from the same centre found that only 12.3% of MRI scans were abnormal, but in this sample the mean age was 26 (compared to 44.5 for our comparison group) and all were under evaluation for first-episode psychosis.{39} It seems likely that the older age and greater disease severity of our comparison 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 is consistent with there being a basic neurological 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.

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Conflicts of interests

MSZ reports receiving personal fees from UCB Pharma for lecturing, outside the submitted work. MAM is in receipt of grant funding from H.Lundbeck A/S and Sosei Heptares, unrelated to this work.

Data availability

Data are owned by a third party, Maudsley Biomedical Research Centre (BRC) Clinical Records Interactive Search (CRIS) tool, which provides access to anonymised data derived from SLaM electronic medical records. These data can only be accessed by permitted individuals from within a secure firewall (i.e. the data cannot be sent elsewhere), in the same manner as the authors. For more information please contact: cris.administrator@slam.nhs.uk.

Contributions

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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Tables

Table 1: Demographic and disease-related characteristics of catatonia and comparison groups. Odds ratios are odds ratios of a catatonia diagnosis.

	Catatonia group (*N* = 79)		**Comparison 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

[a] Calculated for age in decades

Table 2: Numbers of normal and abnormal scans in catatonia and comparison groups.

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

Table 3: Abnormalities by lateralisation, localisation and pathology: number of scans in each group that had at least one abnormality with the specified properties. Each scan may appear in more than one category, e.g. a scan may have a midline and a right-sided abnormality.

	Catatonia group (*N*=79)		**Comparison 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

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461 # Figures

462 Figure 1: Selection of cases and comparison group