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Demographic, clinical and neuroimaging markers of post-stroke emotionalism: A preliminary investigation

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ABSTRACT

Introduction: Post stroke emotionalism (PSE) is a common but poorly understood condition. The value of altered brain structure as a putative risk factor for PSE alongside routinely available demographic and clinical variables has yet to be elucidated.

Methods: 85 patients were recruited from acute inpatient settings within 2 weeks of stroke. PSE was diagnosed using a validated semi-structured interview and standardised measures of stroke severity, functional ability, cognition, mood and quality of life were obtained. Neuroimaging variables (intracranial volume and volumes of cortical grey matter, subcortical grey matter, normal appearing white matter, cerebrum, cerebrospinal fluid and stroke; white matter hyperintensities; and mean cortical thickness) were derived using standardised methods from Magnetic Resonance Imaging (MRI) studies. The relationships between PSE diagnosis, brain structure, demographic and clinical variables were investigated using machine learning algorithms to determine how well different sets of predictors could classify PSE.

Results: The model with the best performance was derived from neuroradiological variables alone (sensitivity = 0.75; specificity = 0.8235), successfully classifying 9/12 individuals with PSE and 28/34 non-PSE cases.

Conclusions: Neuroimaging measures appear to be important in PSE. Future work is needed to determine which specific variables are key. Imaging may complement standard behavioural measures and aid clinicians and researchers.

1. Introduction

Emotional lability, the lessening of control over emotional expression such that individuals cry or laugh in response to minimally sad or humorous stimuli, can arise as a consequence of different neurological conditions, the most common being stroke [1,2]. Post-stroke emotionalism (PSE) affects one in five stroke survivors in the acute phase and one in seven post acutely [3]. Despite being a prevalent condition, the underlying mechanisms of PSE are not well understood.

From a psychological perspective, the ways individuals cope with emotional outbursts may impact the *duration* of PSE episodes [4,5], and poor social support the *persistence* of the disorder [6]. Psychological factors however do not explain why PSE develops in the first place. Individual characteristics such as gender have been associated with PSE, for example PSE may be more common in women [2,7], but sex differences have not been replicated in multivariate analysis [8]. Associations between the clinical characteristics of stroke survivors and PSE have received more attention. Depression scores are higher [9], and the diagnosis of clinical depression more common [4,10,11] in individuals with PSE. Also, PSE is more prevalent in individuals with strokes that result in cognitive impairment, particularly frontal executive dysfunction [1,12–14], suggesting a neurological or neuropsychological basis to the condition. This has been supported by several investigations of the neuroanatomy of PSE. Lesions to frontal and subcortical regions [7], and to cerebellum and brainstem structures [1,7,13] are common findings for example. Disruption to the serotonergic system [15] and dysfunction

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of cerebropontocerebellar pathways [13,16], particularly modulation of descending pathways from frontal and motor cortex to brainstem structures [1] have also been implicated.

What is not yet clear is the value of neuroradiological measures alongside demographic and clinical data. In the current study, we used prediction models incorporating demographic, clinical and brain imaging data to determine whether a classification of PSE, diagnosed by clinical interview in a well defined series of individuals with stroke, is associated with a combination of non-radiological and radiological variables. Specifically, we wished to determine whether measures of gross brain integrity are putative risk factors when considered alongside routinely collected non-radiological clinical stroke data.

2. Materials and methods

2.1. Participants

Participants were recruited between 1 October 2015 and 30 September 2018 within two weeks of stroke from acute stroke units in nine hospitals in Scotland, UK as part of a longitudinal investigation of the epidemiology of PSE (the TEARS (Testing Emotionalism After Recent Stroke) study; NRS Research Network ID 18980). All participants were male or non-pregnant female, ≥18 years of age, with a confirmed clinical diagnosis of ischaemic or haemorrhagic stroke. Individuals scoring <25 on the Frenchay Aphasia Screening Test [17] were excluded, as were individuals with subarachnoid haemorrhage, extra axial bleed, or Transient Ischaemic Attack (TIA). Individuals with severe concurrent medical conditions or with life expectancy <3 months were excluded also. All participants gave written informed consent or else had a proxy provide written consent on their behalf.

PSE was diagnosed using a semi-structured interview, the TEARS - Diagnostic Interview (TEARS-IV). TEARS-IV comprises four sections on post-stroke crying: screen questions, case characteristics, frequency and impact. It has been validated in this population and is based on consensus diagnostic criteria for PSE [18,19]. These comprise: (1) increased tearfulness, (2) crying coming on suddenly with no warning, (3) crying not under usual social control, and (4) crying episodes occurring at least weekly [18]. The interview was administered by specialist stroke nurses who received training from a clinical psychologist and a liaison psychiatrist with expertise in stroke. Other interview-based assessments were the Abbreviated Mental Test [20] (AMT; a measure of cognition), Barthel Index [21] (BI; a measure of functional ability), Hospital Anxiety and Depression Scale [22] (HADS; a measure of mood), Euro-QoL [23] (EQ5D; a quality of life measure) and the National Institute of Health Stroke Scale [24] (NIHSS; a measure of stroke severity). A measure of social deprivation, the SIMD (Scottish Index of Multiple Deprivation [25] was recorded for each participant.

Ethical approval for TEARS was provided by Scotland A Research Ethics Committee (IRAS Reference 157483).

2.2. Brain MRI acquisition and processing

Standard axial fluid attenuated inversion recovery (FLAIR) and 3D volumetric T1 sequences were obtained from NHS picture archiving communication systems (PACS) when available from routine (1.5T or 3T) clinical scanning. White matter hyperintensity (WMH) volumes were segmented using a previously described method [26]. Briefly, a population norm was transferred [27] to each participant to provide an approximation of white matter volume. Hyperintense outliers on FLAIR were identified by transforming each voxel to a standard (z) score. Voxels with $z \geq 1.5$ and within the approximated white matter volume were initially defined as WMHs. This initial estimate of WMH volume was smoothed with a 3D Gaussian kernel to reduce noise and account for partial volumes around WMH edges. Finally, these automated WMH estimates were visually checked and stroke infarcts removed by a trained image analyst (blinded to all other patient information) following STRIVE guidelines [28]. Additionally, hyperintensities were segmented using the automated lesion prediction algorithm [29], as implemented in the Lesion Segmentation Toolbox (LST) version 3.0.0 for SPM [30]. As this was a clinical dataset, not all cases had both T1 and FLAIR images; therefore we used the the lesion prediction algorthim [29] where the T1 was included as a reference if available. Outputs were visually inspected to check for gross anomalies. Normal-appearing tissues, including cortical grey matter and cerebral white matter, and supratentorial cerebrospinal fluid were segmented using tissue norms, within-patient MRI intensities, and adjoining voxel data [31,32]. Cortical thickness was measured from normal appearing tissue volumes using a previously described method [33]. Table 1 provides an explanation of the brain variables used in the study.

All neuroimaging scans were normalised to Montreal Neurological Institute (MNI) space using a modified version of the segmentation algorithm in Statistical Parametric Mapping software (SPM12); [34] details of the procedure are described elsewhere [35]. The dataset comprises participants with T1, FLAIR or both scans; we used T1 data when they were available, otherwise FLAIR images were used. All images in standard space were visually inspected. Lesion segmentation outputs from LST were spatially normalised to MNI space using the transforms from the normalisation procedure and used to determine lesion load (proportion of overlap between lesion and atlas region of interest [ROI]). The atlas consisted of cortical and subcortical regions from the Harvard–Oxford atlas [36] and white matter regions from Johns Hopkins University (131 ROIs in total) [37]. In order to reduce the number of predictors in an unbiased way, we first remove variables with zero variance and then applied a varimax rotated principal component analysis to remaining lesion load features. Components with eigenvalues greater than 1 were extracted for use in subsequent classification analyses.

2.3. PSE classification

There are many algorithms (or inducers) to tackle classification problems, with no clear guidelines about which to select for specific problems. We made use of different algorithms available in the MATLAB 2019a Classification Learner application (for a similar approach see [38]): decision trees with (1) fine (100 branches), (2) medium (20 branches) and (3) coarse (4 branches); (4) linear and (5) quadratic multiple regression; (6) logistic regression; naïve Bayes with (7) Gaussian and (8) kernel density support; support vector machines with (9) linear, (10) quadratic, (11) polynomial order 3, and Gaussian kernels scales of (12) 0.5, (13) 1.7 and (14) 6.9; nearest neighbour classifiers using (15) fine (1), (16) medium (10), and (17) coarse (100) neighbours and distance determined using (18) cosine, (19) cubic and (20)

Table 1
Location non-specific brain variables used in modelling.

Variable	Explanation
Intracranial volume	Volume of the brain and surrounding fluid
Cortical grey matter volume	Volume of grey matter around the edge of the brain
Subcortical grey matter volume	Volume of grey matter in the middle of the brain
Normal appearing white matter	White matter that looks normal
Cerebrum volume	Volume of the cerebrum (whole brain minus cerebellum)
Cerebrospinal fluid volume	Volume of fluid encasing the brain
White matter hyperintensities P	Hyperintensities (bright spots) in the white matter expressed as a proportion (P) of intracranial volume
White matter hyperintensity volume	Volume of hyperintensities (bright spots) in the white matter
Stroke volume	Volume of stroke
Mean cortical thickness	Average thickness of the cortex (grey matter around the edge of the brain)

Euclidean distance; ensembles using (21) adaptive (Ada) boosted trees, (22) bagged trees, (23) subspace with discriminant learner, (24) subspace with nearest neighbour learner and (25) random under sampling (RUS) boosted trees.

2.4. Model building

We built seven models in total in order to evaluate the performance of a range of predictors. As there were incomplete data for certain features, the sample size per model varied. We chose not to use minimum complete datasets (i.e. exclude cases that had any missing data) as this would have reduced sample size. The sample size and features were as follows: (1) demographics (age, gender and SIMD; $n = 71$); (2) clinical assessments (AMT, BI, EQ5D HADS; $n = 67$); (3) summary of neuroimaging variables (all location non-specific: intracranial volume, cerebrum volume, cerebrospinal fluid (CSF) volume, white matter hyperintensity, white matter hyperintensity volume, stroke volume and segmented lesion volume using LST; $n = 46$); (4) principal components of lesion load (which differs from the previous model in incorporating lesion location information; $n = 58$); (5) combining demographic and clinical data from models 1 and 2 ($n = 65$); (6) combining all brain variables from model 3 and 4 ($n = 46$); and (7) combining all variables ($n = 41$). For each model, the dependent variable was PSE diagnosis.

We used five-fold cross validation to evaluate the models, whereby 80% of the data is used for training and the model is tested on the remaining 20%. For each model, we obtained balanced accuracy, area under the curve, and specificity and sensitivity values. Model inference was determined using permutation testing ($n = 1000$), where on each permuted iteration the dependent variable was shuffled and model performance re-calculated for the null hypothesis (no relationship between predictors and dependent variable). Models were considered significant if the observed balanced accuracy survived $p < 0.05$. In order to determine variability in the performance, we also repeated the analysis 50 times where on each iteration the fold membership changed. A Wilcoxon test was conducted on the outcome of the 50 iterations between each model type, where differences in performance ($p < 0.05$) indicated overall advantage for a particular set of predictors.

3. Results

3.1. Patient characteristics

Brain imaging data were obtained for 85 participants. As shown in Table 2, those recruited for imaging were, in general, younger, less impacted by their stroke (higher BI and lower NIHSS scores), less likely to have dementia (AMT higher), and less likely to have a total anterior circulation (TAC) stroke. Individuals with and without imaging data were similar in age, sex and in frequency of PSE.

Table 3 shows demographic and clinical data on participants stratified by PSE status ($n = 20$ with PSE, $n = 53$ with no PSE and $n = 12$ whose PSE status was unknown). The only differences between individuals with and without PSE were in mood and functional ability: depression scores on the HADS (possible range 0–21) were 2.3 points higher for individuals with PSE ($p = 0.030$) and anxiety scores (same range) were 4.5 points higher ($p = 0.001$), and those with PSE were marginally less functionally impaired ($p = 0.041$). No single brain imaging variable differentiated the groups.

3.2. Classification models

The proportion of individuals with and without a diagnosis of PSE per model was as follows: (1) 19/52; (2) 20/47; (3) 12/34; (4) 14/44; (5); 19/46 (6); 12/34 and (7) 12/29.

In the first instance, for each model configuration (1–7) we selected the inducer (out of 25 inducers) that produced the numerically highest area under the curve (AUC), which was equivalent to balanced accuracy.

Table 2
Patient characteristics cross-classified by recruitment to MRI imaging.

		No imaging	MRI imaging	*p*-value
N		192	85	
Age at stroke (mean (SD))		68.02 (14.44)	62.21 (13.97)	0.002
Sex (n (%))	Female	85 (44.3)	37 (43.5)	0.999
	Male	107 (55.7)	48 (56.5)	
SIMD rank (mean (SD))		2749.97 (2031.49)	2702.91 (2032.78)	0.861
PSE (n (%))	No PSE at T0	113 (58.9)	53 (62.4)	0.584
	PSE at T0	42 (21.9)	20 (23.5)	
	PSE at T0 unknown	37 (19.3)	12 (14.1)	
TEARS Score (mean (SD))		2.81 (4.55)	2.17 (4.08)	0.303
BI (mean (SD))		14.90 (5.69)	17.58 (4.08)	<0.001
AMT (mean (SD))		18.04 (3.32)	19.01 (2.23)	0.021
HADS depression (mean (SD))		4.85 (4.17)	3.79 (3.37)	0.054
HADS anxiety (mean (SD))		5.51 (4.47)	5.82 (4.76)	0.621
Education (n (%))	Secondary	129 (70.5)	50 (65.8)	0.260
	University	28 (15.3)	14 (18.4)	
	Other	20 (10.9)	12 (15.8)	
NIHSS (mean (SD))		6.60 (6.00)	3.56 (3.48)	0.006
Stroke type (n (%))	Infarct	171 (89.1)	78 (94.0)	0.292
	Haemorrhage	21 (10.9)	5 (6.0)	
Oxford class (n (%))	TAC	20 (11.0)	2 (2.4)	0.001
	PAC	78 (42.9)	23 (27.4)	
	LAC	53 (29.1)	31 (36.9)	
	POC	31 (17.0)	28 (33.3)	

Notes: AMT Abbreviated Mental Test; BI Barthel Index; HADS Hospital Anxiety and Depression Scale; LAC Lacunar; MRI Magnetic Resonance Imagine; NIHSS National Institute of Health Stroke Scales; PAC Partial Anterior Circulation; POC Posterior Circulation; PSE Post Stroke Emotionalism; SD Standard Deviation; SIMD Scottish Index of Multiple Deprivation; TAC Total Anterior Circulation; TEARS Testing Emotionalism After Recurrent Stroke.

All models performed significantly better than chance. The first 'demographic' model (age, sex and SIMD) produced an AUC of 0.5262 ($p < 0.001$) using a nearest neighbour classifer (with fine neighbours). The corresponding sensitivity and specificity figures were 0.2632 and 0.7692, respectively. The second 'clinical' model (depression and cognition scores) produced an AUC of 0.6468 ($p < 0.001$) (sensitivity = 0.4; specificity = 0.8936) but combining variables from models 1 and 2 did not improve the model, although it was still significantly better than chance (AUC 0.6453, $p < 0.001$) (sensitivity = 0.4211; specificity = 0.8696). The model with the best performance (mean highest AUC) resulted from brain summary variables alone, producing an AUC of 0.7868 ($p < 0.001$) (sensitivity = 0.75; specificity = 0.8235): this represents successfully classifying 9/12 PSE and 28/34 non-PSE cases. The next best performing model was observed using the brain summary variables and lesion load variables, which produced a mean AUC of 0.7255 ($p < 0.001$) (sensitivity = 0.8333, specificity = 0.6176). The model performance was not improved by using the lesion load variables alone (AUC = 0.6834, $p < 0.001$, sensitivity = 1; specificity = 0.1591) nor by combining all variables (demographic, clinical and neuroradiological) together (AUC = 0.6983, $p < 0.01$, sensitivity = 0.5; specificity = 0.8966).

We repeated this analysis by using the minimum complete datasets ($n = 41$) for all models. In this analysis, we found model performance increased as the model variable set increased; model 1 (median AUC = 0.5783) and 2 (median AUC = 0.6257) showed a relatively large increase between models but performance plateaued from model 3 (median AUC = 0.6667) to 7 (median AUC = 0.6925).

Finally, in order to compare model performance against each other, we iteratively generated model outputs 50 times, where on each iteration the subject fold allocation was randomly shuffled (see Fig. 1). It was

Table 3
Patient characteristics stratified by PSE status.

		No PSE	PSE	Unknown	p-value
N		53	20	12	
Age at stroke (mean (SD))		63.57 (14.19)	55.30 (11.02)	67.75 (14.16)	0.024
Sex (n (%))	Female	22(41.5)	10 (50)	5 (41.7)	0.800
	Male	31 (58.5)	10 (50)	7 (58.3)	
SIMD rank (mean (SD))		2589.31 (1977.78)	2349.42 (1885.30)	3965.30 (2312.37)	0.100
BI (mean (SD))		17.83 (3.70)	18.50 (2.21)	14.92 (5.99)	0.041
AMT (mean (SD))		19.29 (2.29)	18.50 (2.21)	18.33 (1.37)	0.300
HADS-DEP (mean (SD))		3.19 (3.06)	5.50 (3.86)	3.33 (2.73)	0.030
HADS-ANX (mean (SD))		4.46 (3.68)	8.95 (6.11)	7.17 (2.99)	0.001
Education (n (%))	Secondary	32 (65.3)	13 (68.4)	5 (62.5)	0.909
	University	8 (16.3)	4 (21.1)	2 (25)	
	Other	9 (18.4)	2 (10.5)	1 (12.5)	
NIHSS (mean (SD))		2.53 (1.87)	4.60 (4.88)	4.86 (4.18)	0.173
Stroke type (n (%))	Infarct	50 (94.2)	19 (95)	11 (90.9)	0.893
	Haemorrhage	3 (5.8)	1 (5.0)	1 (9.1)	
Oxford class (n (%))	TAC	1 (1.9)	0 (0.0)	1 (8.3)	0.144
	PAC	12 (23.1)	6 (30.0)	5 (41.7)	
	LAC	18 (34.6)	11 (55.0)	2 (16.7)	
	POC	21 (40.4)	3 (15.0)	4 (33.3)	
T1 (mean (SD))		0.42 (0.50)	0.35 (0.49)	0.17 (0.39)	0.276
FLAIR (mean (SD))		0.83 (0.38)	0.70 (0.47)	0.58 (0.51)	0.144
Intracranial volume (mean (SD))		1396.05 (152.77)	1444.09 (146.74)	1379.46 (98.10)	0.473
Cortical grey matter volume (mean (SD))		466.59 (76.39)	497.58 (49.71)	416.06 (9.16)	0.328
Subcortical grey matter volume (mean (SD))		31.74 (4.95)	35.14 (2.62)	30.99 (1.52)	0.210
Normal appearing white matter (mean (SD))		470.07 (106.14)	496.12 (83.53)	431.53 (19.92)	0.694
Cerebrum volume (mean (SD))		974.26 (119.05)	1013.05 (114.84)	946.26 (61.83)	0.360
Cerebrospinal fluid volume (mean (SD))		255.12 (54.167)	244.72 (38.55)	261.94 (63.81)	0.711
White matter hyperintensities P (mean (SD))		9.16 (14.27)	2.79 (2.45)	10.67 (16.62)	0.244
White matter hyperintensity volume (mean (SD))		20.94 (21.86)	9.05 (6.91)	24.15 (24.72)	0.124
Stroke volume (mean (SD))		5.97 (12.68)	0.83 (0.85)	7.08 (7.48)	0.319
Mean cortical thickness (mean (SD))		2.49 (0.16)	2.43 (0.20)	NaN (NA)	0.552

Notes: AMT Abbreviated Mental Test; BI Barthel Index; HADS Hospital Anxiety and Depression Scale; FLAIR Fluid-attenuated Inversion Recovery; LAC Lacunar; MRI Magnetic Resonance Imagine; NIHSS National Institute of Health Stroke Scales; PAC Partial Anterior Circulation; POC Posterior Circulation; PSE Post Stroke Emotionalism; SD Standard Deviation; SIMD Scottish Index of Multiple Deprivation; T1 Longitudinal Relaxation Time; TAC Total Anterior Circulation; TEARS Testing Emotionalism After Recurrent Stroke.

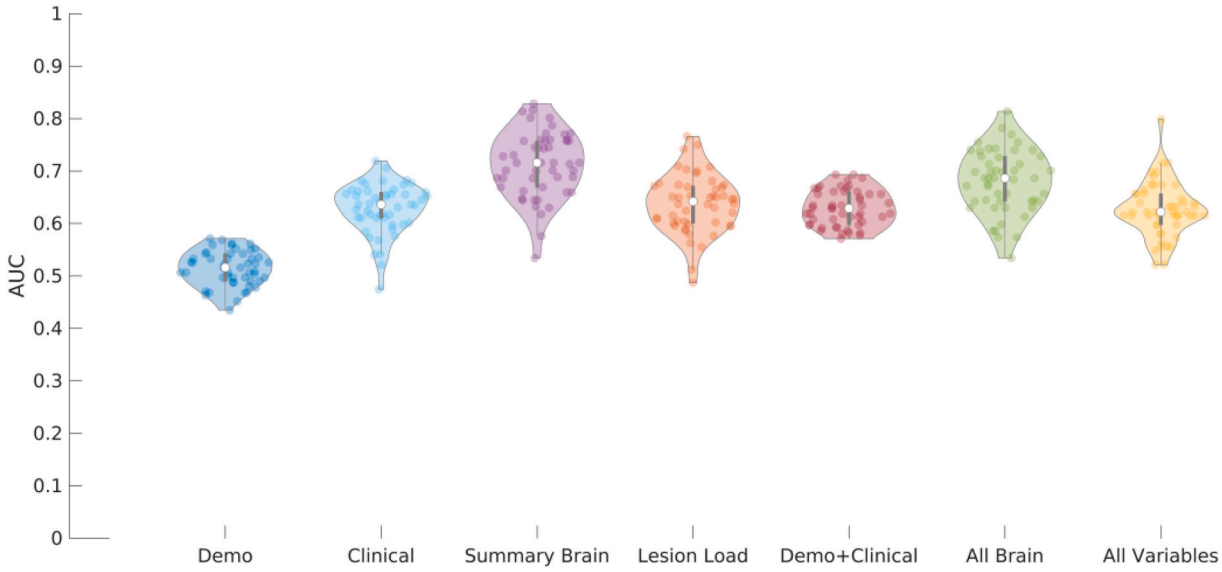

Fig. 1. Variation in model performance for each of the highest performing configurations.

found that model 3 (neuroradiology summary variables) produced a significantly higher AUC than all other models (Wilcoxon test: $Zs > 5.471$), except all brain variables (Wilcoxon test: $Z = 2.849$). The demographic model was significantly worse than all other models, whereas the clinical model was similar to lesion load (and combinations of demographic, clinical and all other variables).

4. Discussion

We have shown that the classification of PSE can be made more accurately using a summary measure of radiological data obtained from routine clinical imaging than it can from either demographic variables or measures of depression and cognitive performance, though all models did perform better than chance. Although previous studies have

investigated group differences between individuals with and without PSE on clinico-demographic and neuroimaging variables, they have addressed only whether a feature stands out between groups, not the specific value of that feature in distinguishing between these individuals. This is because the situation is possible whereby a feature is more common in one group than another, but is not useful as a predictor overall because it might be relevant for a small – albeit statistically significant – subset of cases. In contrast, we tested the utility of features by conducting cross-validated prediction models and our approach determined how well predictive models generalise to new cases.

The model with the best fit comprised brain summary variables. These variables were, in general terms, location non-specific, suggesting that the overall structure and health of the brain may be important in determining the presence of PSE. This finding corresponds with previous studies demonstrating that lesions in a wide range of brain areas, in individuals with different types of stroke, are associated with the condition [16]. This is an important finding for at least three main reasons. Firstly, in stroke care settings, knowledge of risk factors can help clinicians identify individuals at greatest likelihood of developing PSE. PSE is reported to be both under-recognised and under-treated [39]. Secondly, awareness that brain integrity tends to be less good in individuals with PSE can help clinicians plan for treatment and management of the condition itself. In a recent study [40], experienced stroke professionals reported frequent use of a range of non-pharmacological interventions for PSE, including 'provide education', 'teach relaxation techniques' and 'modify patient beliefs (thought challenge)'. These particular techniques require new learning and cognitive flexibility, as well as the motivation and drive to apply them, and they are likely to be problematic for a proportion of individuals who experience PSE in the context of marked damage to the brain. Clinicians may need to adapt non-pharmacological interventions, perhaps simplifying materials, or else providing more opportunities for learning and consolidation. Thirdly, researchers should consider radiological data when assigning individuals to different treatments in intervention evaluation studies, perhaps stratifying for brain health, or controlling for its possible impact on outcome in intervention study analyses.

This study was limited by the relatively small number of participants with full imaging and clinical data, and the small number of participants overall. Though stroke patients were drawn from a large sample recruited consecutively from multiple acute hospital sites with detailed clinical interviews and a comprehensive range of clinical assessments, those who received MRI brain scans were not fully representative of all stroke patients recruited to the study. Individuals who underwent magnetic resonance imaging were more likely to have less severe strokes. That said, 25% of the sample had PSE, a similar figure to the 17% (95% CI 12–24%) found in a meta-analytic review of PSE prevalence in the acute phase post stroke [3]. Our figure may a little higher because our participants were recruited within two weeks of stroke as opposed to the 0–4 week interval in the meta-anlaytic study. We acknowledge that the models may not be generalisable to stroke survivors at later, less acute stages of recovery. Intriguingly, it has been shown that although PSE is closely related to neurochemical changes associated with specific brain regions immediately after stroke, poor social support is a better predictor of PSE than brain related variables three months post stroke [6]. Future work should aim to investigate the relative importance of psychosocial variables and brain integrity in individuals for whom PSE is a chronic rather than acute condition. Brain integrity should include the presence or absence of microhaemorrhages, which were shown to be a pathomechanism of PSE in a Chinese sample recruited less acutely than the sample in our study [41]. Note should be made of psychoactive medication prescription. A recent Cochrane review found that antidepressants (of a variety of drug classes) reduce emotionalism after stroke, and so this may have an impact on the prevalence and severity of PSE [39]; we did not record the use of these medications in our sample.

In summary, our results suggest that the integrity of the brain determines, at least in part, who does and does not experience PSE following stroke. Althought the accuracy with which neuroimaging data classified PSE may be less good than required for clinical translation – in the best of our models just three in every four individuals with PSE were correctly classified – these data do appear to complement standard clinical-behavioural measures.

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Declaration of Competing Interest

The authors declare no competing interests.

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