

# 1 Deep structural brain lesions associated with consciousness

## 2 impairment early after haemorrhagic stroke

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10

11    **Authors Contributions**

12    Study concept and design: BR, KD, ASR and JC. Data collection: ASR, KI, CC, AM and  
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16    Statistical analysis: BR, KD, CMM, GL and JC. Study supervision: CC, AM and AV. BR,  
17    KD and JC had full access to all the data in the study and take responsibility for the  
18    integrity of the data and the accuracy of the data analysis.

## 1 Abstract

2 **Background:** The significance of deep structural lesions on level of consciousness  
3 early after intracerebral haemorrhage (ICH) is largely unknown.

4 **Methods:** We studied a consecutive series of patients with spontaneous ICH that  
5 underwent MRI within 7 days of the bleed. We assessed consciousness by testing for  
6 command following from time of MRI to hospital discharge, and determined 3-months  
7 functional outcomes using the Glasgow Outcome Scale-Extended (GOS-E). ICH and  
8 oedema volumes, intraventricular haemorrhage (IVH), and midline shift (MLS) were  
9 quantified. Presence of blood and oedema in deep brain regions previously implicated  
10 in consciousness were assessed. A machine learning approach using logistic  
11 regression with elastic net regularization was applied to identify parameters that best  
12 predicted consciousness at discharge controlling for confounders.

13 **Results:** From 158 ICH patients that underwent MRI, 66% (N=105) were conscious and  
14 34% (N=53) unconscious at the time of MRI. Almost half of unconscious patients (49%,  
15 N= 26) recovered consciousness by ICU discharge. Focal lesions within subcortical  
16 structures predicted persistent impairment of consciousness at discharge together with  
17 MLS, IVH, and ICH and oedema volumes (AUC 0.74; 95%-CI 0.73-0.75). Caudate  
18 nucleus, midbrain peduncle, and pontine tegmentum were implicated as critical  
19 structures. Unconscious patients predicted to recover consciousness had better 3-  
20 month functional outcomes than those predicted to remain unconscious (35% vs 0%  
21 GOS-E ≥4; p-value=0.02).

22 **Conclusion:** MRI lesions within key subcortical structures together with measures  
23 reflecting the mass effect of the haemorrhage (lesion volumes, IVH, MLS) obtained

- 1 within one week of ICH can help predict early recovery of consciousness and 3-month
- 2 functional outcome.

## 1    **Introduction**

2    Insights into mechanisms underlying early and delayed recovery of consciousness  
3    following brain injury are limited. Investigators have implicated several subcortical  
4    structures to be crucial for maintenance of arousal such as pontine tegmentum,  
5    midbrain, basal forebrain, hypothalamus and central thalamus [1–3]. Structures  
6    important for conscious processing or awareness include sub-cortical regions (i.e.,  
7    thalamus, putamen, caudate and pallidum) as well as associative cortical regions (i.e.,  
8    prefrontal, temporal and parietal cortices) and their connecting neuronal pathways [4–9].  
9    Based on neuropathological, imaging and electrophysiological studies, circuit models  
10   have been developed that help conceptualize impairment and recovery of  
11   consciousness (e.g., modern concepts of the ascending reticular activating pathway  
12   [ARAS],[3,10,11] mesocircuit model,[6,12] and global neuronal workspace[5]). Structural  
13   damage to regions within this circuitry (e.g., large intracerebral haemorrhage [ICH] in  
14   the thalamus) as well as lesions that functionally affect circuit connectivity (e.g.,  
15   stretching thalamo-cortical projections from mass effect), especially when they are  
16   bilateral, may result in clinically indistinguishable unconscious patients. However,  
17   depending on the anatomical location and the pathophysiological mechanism of lesions,  
18   prognosis for recovery of consciousness can dramatically differ [13].

19        Here we studied patients with ICH, a condition that may cause both focal injury to  
20   specific subcortical brain regions that are integral parts of the ARAS and/or the  
21   mesocircuit model as well as more diffuse injury that can impair network connectivity  
22   (e.g., from midline shift and/or oedema) [14]. Specifically, we explored how the level of  
23   impairment and recovery of consciousness relate to the locations and the extent of

1 subcortical injury quantified by early MRI. We tested the hypothesis that focal lesions  
2 within subcortical regions included in the previously mentioned models of  
3 consciousness, in addition to established characteristics of the haemorrhage (i.e.,  
4 volume of ICH and oedema, and midline shift [MLS]), contribute to consciousness level  
5 during the acute phase of ICH.

## 6 Methods

### 7 Subjects

8 We studied a consecutive series of patients with ICH that underwent MRI including fluid  
9 attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI) within one  
10 week of the ICH between March 2009 and November 2015. Inclusion criteria were: (1)  
11 spontaneous ICH, and (2) MRI obtained within 7 days of the haemorrhage. Exclusion  
12 criteria were: (1) age <18 years, (2) pregnancy, (3) ICH due to tumour, trauma, or  
13 haemorrhagic conversion of an ischemic stroke, and (4) patients or families who  
14 declined to participate in the study. Patient management was in accordance with current  
15 guidelines (Supplementary Material). Data were collected as part of a prospective  
16 observational cohort study approved by the local institutional review board. Written  
17 informed consent was obtained from patients and/or legal surrogates.

18

### 19 Clinical variables

20 We collected baseline demographic and medical history (e.g., age, gender, race), and  
21 admission characteristics of the ICH (e.g., ICH volume and location, presumed  
22 aetiology, intraventricular haemorrhage, primary ICH-score)<sup>8</sup>. We calculated the  
23 admission Functional Outcome in Patients With Primary Intracerebral Hemorrhage

1 (FUNC) score by quantifying ICH volume and location, age, Glasgow Coma Scale, and  
2 pre-ICH cognitive impairment.[16] Daily assessments included documentation of  
3 seizures (as per hospital protocol all unconscious patients undergo continuous EEG  
4 monitoring for at least 24 hours), metabolic abnormalities (e.g., renal function and liver  
5 failure), and fever. Doses of all sedatives and laboratory values were recorded at the  
6 time of all behavioural assessments.

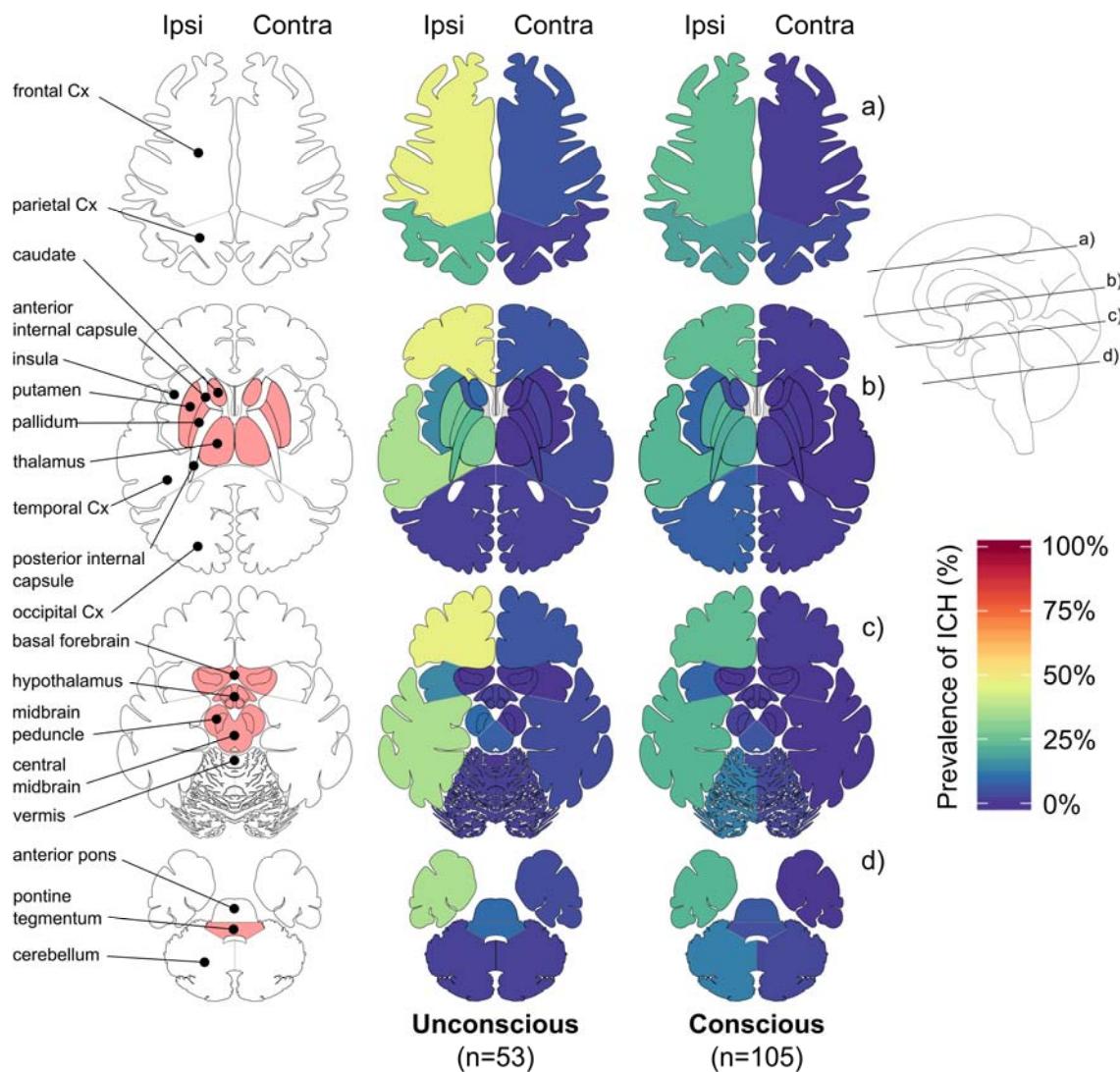
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### 8 **Behavioural assessment**

9 We assessed level of consciousness daily from ICU admission to 30 days post-injury or  
10 hospital discharge, whichever was sooner. As described previously [17], behavioural  
11 assessments of consciousness were performed during morning rounds. These  
12 consisted of protocolized, hierarchical assessments categorizing consciousness into  
13 three levels of behavioural states: (1) “comatose” (no response to stimulation), (2)  
14 “arousable” (opening eyes and/or attending to stimulation), or (3) “conscious” (following  
15 simple commands; e.g., “show me two fingers”). To overcome language impairment or  
16 aphasia while testing for consciousness, we used in addition to verbal commands, non-  
17 verbal cues to induce mimicking (e.g., holding up two fingers and then gesturing to  
18 subject’s supported hand). For the classification approach described below, we  
19 dichotomized patients into “conscious” (category 3, following verbal and/or non-verbal  
20 commands) and “unconscious” (categories 1 and 2; see details in supplementary  
21 Material). According to our ICU protocol daily assessments were performed during  
22 interruption of sedation.

1  
2 **MR acquisition**  
3 As part of our clinical protocol we acquired MR images within 7 days of haemorrhage  
4 whenever deemed safe by the attending neurointensivist using a 3T scanner (GE Signa  
5 HDx MRI scanner; HD23 software). Total acquisition time did not exceed 45 minutes.  
6 We obtained FLAIR, T1-weighted, and DWI sequences (for details please refer to the  
7 supplementary material section).

8  
9 **Categorization of lesions**  
10 Anatomical regions of interest (ROIs) were predefined based on established  
11 neuroanatomical atlases [18] with a focus on subcortical brain regions (henceforth  
12 referred to as “subcortical ROIs”) previously implicated in consciousness [1–7,12]. A  
13 board-certified neurologist (AR) categorized the presence of blood and perihematomal  
14 FLAIR hyperintensity (henceforth referred to as “oedema”) for each ROI based on a 3D  
15 visualization of FLAIR, T1 and DWI sequences. The following ROIs were included in the  
16 models: pontine tegmentum, midbrain (central and peduncles), hypothalamus, basal  
17 forebrain, thalamus, pallidum, putamen, and caudate nuclei (see Figure 1, 1<sup>st</sup> row in  
18 pink colour). For purposes of analysis, lesion laterality was reclassified from right/left  
19 into ipsi/contralateral using the following approach. The side of the brain with the larger  
20 amount of blood was labelled as ipsilateral. The side with the smaller amount was  
21 labelled as contralateral. Intraventricular haemorrhage (IVH) was assessed in the 3<sup>rd</sup>,  
22 4<sup>th</sup>, and each lateral ventricle and classified as present or absent. Any challenging  
23 cases with bilateral haemorrhage were classified by consensus between three board  
24 certified neurologists (AR, JC, BR). A board-certified neurologist (DR) coded the same



1  
2 **Figure 1. Anatomical segmentation, subcortical ROIs and location of**  
3 **haemorrhages according to consciousness level.** Anatomical segmentation is  
4 represented on the left pane with the explored subcortical regions of interest (ROIs) in  
5 pink. Prevalence of ICH observed on MRI are showed by level of consciousness at the  
6 time of the MRI ("unconscious": patients did not follow or mimic even simple commands;  
7 "conscious": patients followed or mimicked simple commands. "ipsi" and "contra" stand  
8 for ipsilateral and contralateral with respect to the primary side of the haemorrhage; Cx:  
9 cortex.

10

11 imaging parameters on a random 20% sample of MRIs blinded to the first coder's  
12 results. Interrater agreement was assessed using kappa statistics.

1 **Volumetric measurements and midline shift**  
2 Haemorrhage, perilesional oedema, and brain volumes were quantified based on FLAIR  
3 sequences using a semi-automatized method. Briefly, a gross region-of-interest was  
4 identified that encapsulated the affected region (ICH or oedema) to automatically  
5 compute a 3D image that were visually inspected and manually corrected if necessary  
6 (KI, see Supplementary Material and Figure 2 panel A). Midline shift (MLS) was  
7 measured both at the level of the septum pellucidum as well as at the pineal gland, and  
8 the larger number was recorded [19].

9

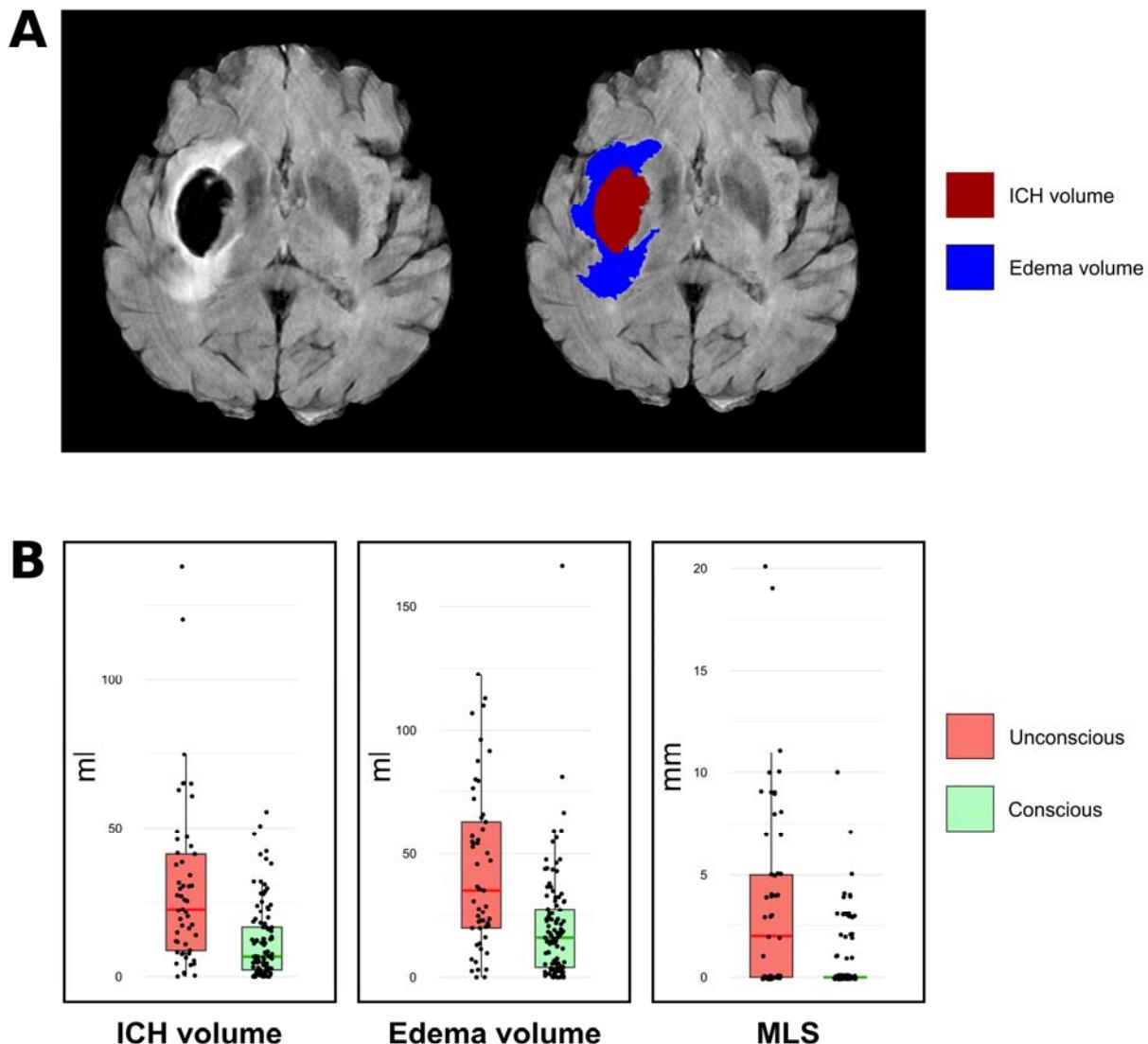
10 **Main outcome**

11 Main outcomes were the level of consciousness observed at time of ICU discharge and  
12 the Glasgow Outcome Scale-Extended (GOS-E) obtained 3 months following the  
13 haemorrhage via phone interviews [20]. As an additional outcome measure, we  
14 recorded the best level of consciousness observed at any time during hospitalization  
15 following MRI acquisition.

16

17 **Confounders**

18 All patients were clinically evaluated for the presence of seizures, hypo- or  
19 hyperglycaemia (70 and 200 mg/dL, respectively), hypo- and hypernatremia (133 and  
20 150 mmol/L, respectively), and renal and fulminant liver failure at the time of  
21 behavioural assessments. All analyses were directly controlled for potential metabolic



1  
2 **Figure 2. Haemorrhage and oedema volumes and midline shift. Panel A.** Illustrates  
3 the volume on MRIs of one exemplary case. **Panel B.** Measurements according to  
4 consciousness level at time of MRI (normalized values; for details please refer to  
5 methods). ICH: Intracerebral Hemorrhage; MLS: midline shift.

6  
7 confounders (including blood urea nitrogen, creatinine, serum glucose level). In addition  
8 to the above outlined protocol of stopping sedation for all behavioural assessments we  
9 collected the cumulative doses of all sedative medications administered within the two  
10 elimination half-lives preceding clinical assessments.[17].

1    **Statistical analysis**

2    A machine learning approach using logistic regressions with elastic net regularization  
3    was applied to identify the parameters that best predicted consciousness at time of MRI  
4    and at time of ICU discharge [21]. This method allows a robust data-driven analysis  
5    when there are a large number of features compared to the number of observed events  
6    and/or when features are highly correlated. Models were trained on the clinical labels  
7    (conscious vs unconscious) obtained either at the time of MRI or at the time of ICU  
8    discharge. In order asses robustness of the model, we performed 5-fold cross  
9    validations repeated 500 times [22]. Model performance was evaluated using the area  
10   under the receiver operating characteristic curve (AUC) with 95% confidence intervals  
11   (95% CI). Logistic regression using elastic net regularization were computed with the  
12   Glmnet R package (for details please refer to the Supplementary Material).

13       Differences in baseline features between the patients that fulfilled inclusion  
14   criteria and those that did not were explored using Fisher's exact test for categorical and  
15   Wilcoxon–Mann–Whitney test for quantitative variables as appropriate. All statistical  
16   tests were two-sided. Categorical variables are reported as percentage (number) and  
17   quantitative variables as median (interquartile range). Significance was set at  $P<0.05$ .  
18   All analyses were performed using the R statistical software version 3.4.1 [23].

19

20    **Results**

21    **Enrolment bias analysis**

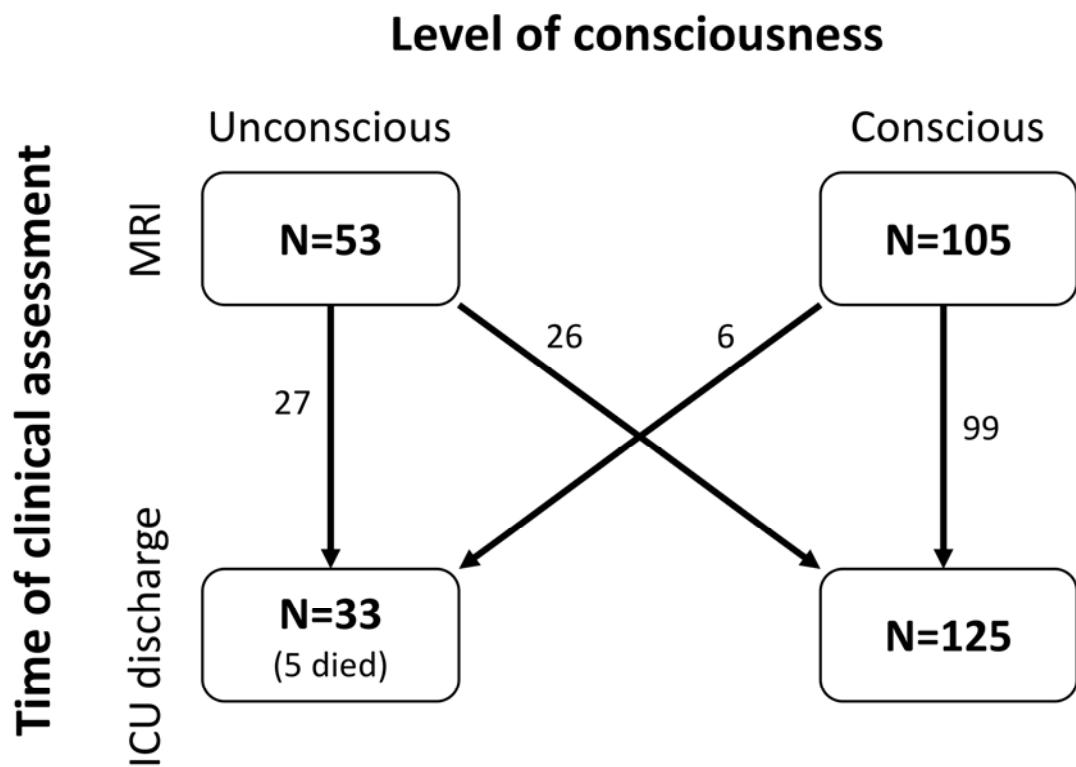
22    From a total of 690 patients admitted during the study period, 23% (N=158) had an MRI  
23    within the 7 days of the haemorrhage and fulfilled the inclusion criteria. Patients

1 included in the study more frequently had presumed amyloid as the underlying  
2 aetiology, lobar location, better admission GCS, primary ICH and FUNC scores, smaller  
3 ICH volumes on the admission CT scan, and better outcomes as reflected in the 3-  
4 months GOS-E, when compared to patients that were not included (Table 1). MRI scans  
5 were obtained within a median of 2 (IQR 1, 3) days from ICH. Main ICH aetiologies  
6 were hypertension (49%; N=78) and amyloid (37%; N=59).

7

### 8 **Patient cohort**

9 From a total of 158 ICH patients, 66% (N=105) were conscious, and 34% (N=53) were  
10 unconscious at the time of MRI (Figure 3). At ICU discharge (occurring on median day 4  
11 [2, 8]), 79% (N=125) were conscious, 18% (N=28) remained unconscious, and 3% were  
12 dead (N=5). 49% (N=26) of initially unconscious patients recovered consciousness at  
13 ICU discharge. 6% (N=6) of the initially conscious patients became unconscious during  
14 the ICU stay. Reasons for secondary unconsciousness included worsening oedema  
15 (N=3), hydrocephalus (N=1), ventriculitis (N=1), and seizures (N=1). At the time of MRI  
16 acquisition and ICU discharge, hypo- or hyperglycaemia, hypo- or hypernatremia, renal  
17 or fulminant liver failure were not present to explain unconsciousness. One patient with  
18 secondary loss of consciousness was seizing prior to death (for the purposes of the  
19 study this was considered the ICU discharge time).



1

2 **Figure 3. Flow chart.** Level of consciousness assessed at MRI and ICU discharge.

3 Note that for the 5 patients who died in the ICU, we considered the last neurological

4 exam as the assessment at ICU discharge (of those that died, 3 patients were

5 unconscious and 2 conscious at time of MRI, all of them were unconscious prior to

6 death).

7

8 At time of MRI scan only 15% (N=24) of patients received any sedative

9 medication (see table S1) and none of the patients received sedatives at ICU discharge.

10 In patients that were unconscious at the time of MRI, propofol had been administered

11 more frequently (19% vs 6%) but at lower cumulative doses (131+/-69 vs 361+/- 202 mg

12 over the 2 preceding half-lives) than those that were conscious.

1    **MRI findings**

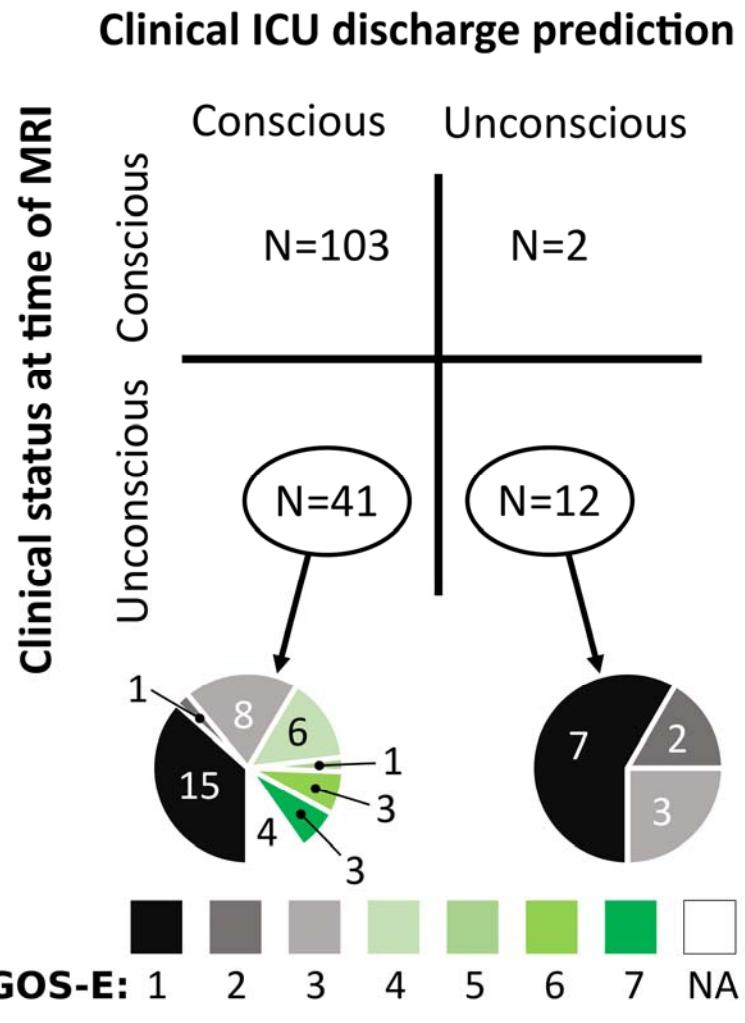
2    73% (N=116) of patients had an isolated unilateral supratentorial ICH whereas 11%  
3    (N=17) had an isolated infratentorial ICH and 7% (N=11) had both (supratentorial and  
4    infratentorial ICH). ICH was most frequently observed in frontal (37%) and temporal  
5    cortices (27%), globus pallidus (23%), thalamus (23%), putamen (22%), posterior limb  
6    of internal capsule (21%), and the parietal cortex (22%, Figure 4). Interrater agreements  
7    for both ICH and oedema measures in all ROIs reached a median kappa of 0.82 (0.66,  
8    0.88).

9            Patients that were unconscious at the time of MRI more frequently had ICH  
10    affecting frontal and temporal lobes as well as the brainstem. Amongst unconscious  
11    patients, ICH was least frequently located in the cerebellum and occipital cortex. Brain  
12    volumes ranged from 1101 to 1887ml (group mean 1451ml). After normalization, ICH  
13    volumes were 11 ml (4, 26), oedema volumes 21 ml (8, 39), and MLS was 0 (0, 3) mm.  
14    ICH volume, oedema volume, and MLS were greater for patients that were unconscious  
15    at time of MRI and at time of ICU discharge when compared to those that were  
16    conscious (Figure 2; Table S2). IVH was more common amongst unconscious patients  
17    at ICU discharge (Table S2).

18

19    **Prediction of consciousness at time of MRI and ICU discharge**

20    The algorithms trained on subcortical ROIs together with ICH and oedema volumes,  
21    MLS and IVH accurately predicted level of consciousness both at the time of MRI and at  
22    ICU discharge (AUC = 0.74 [95%CI: 0.72, 0.75] and 0.74 [95%CI: 0.73, 0.75],  
23    respectively). ICH volume and MLS were the most important predictors (Table 2).  
24    Lesions in pontine tegmentum (oedema), in the ipsilateral caudate nuclei (ICH and



1  
2 **Figure 4. Predicted level of consciousness at ICU discharge based on imaging**  
3 **measures.** Unconscious patients at time of MRI that were predicted to be conscious at  
4 ICU discharge (n=41) based on imaging findings were more likely to be conscious at  
5 ICU discharge and had a greater chance to reach a GOS-E  $\geq 4$  at 3 months (illustrated  
6 in shades of green; p-value = 0.02). GOS-E: Glasgow Outcome Scale – revised; NA:  
7 not available (lost follow-up).

8  
9 oedema), as well as in the contralateral midbrain peduncle, putamen and pallidum  
10 (oedema), were identified as predictors of being unconscious at time of MRI (Table 2;  
11 Figure S1). Lesions in pontine tegmentum (oedema), ipsilateral midbrain peduncle

1 (ICH) and ipsilateral caudate nuclei (ICH and oedema; please refer to the  
2 Supplementary Material for details on these patients) were identified as predictors of  
3 being unconscious at ICU discharge (Table 2; Figure S2). In addition, over both models,  
4 a few ROIs were found to be associated with being conscious (e.g., pallidum, central  
5 midbrain, basal forebrain; see Table 2, Figure S1 and S2 and discussion).

6 Patients unconscious at time of MRI that were predicted to be conscious at ICU  
7 discharge more frequently were arousable than those that were predicted to remain  
8 unconscious, although this difference did not reach statistical difference (61% [N=25/41]  
9 vs 33% [N=4/12]; p-value = 0.1). In univariate analysis, GCS and FUNC scores were  
10 associated with level of consciousness at time of MRI and ICU discharge but primary  
11 ICH score was only associated with level of consciousness at ICU discharge (Table S2).

## 12 **Confounders**

13 The model trained to predict consciousness at the time of MRI retained cumulative  
14 doses of midazolam and fentanyl together with the imaging parameters (Supplementary  
15 Material). However, performance of the models was not improved by including sedative  
16 doses (cumulative or current), cortical and cerebellar ROIs, or measures of metabolic  
17 disarray (i.e., renal insufficiency, glucose level).

18

## 19 **Functional outcome at 3 months**

20 Three-month GOS-E were obtained for 92% (N=145/158) of the patients. Mean GOS-E  
21 was 4 (IQR 1, 6; Table 1), with 53% (N=77/145) of patients having a favourable  
22 outcome (GOS-E  $\geq$  4: 4% GOS-E 8, 19% GOS-E 7, 14% GOS-E 6, 1% GOS-E 5, 14%  
23 GOS-E 4), 19% (N=27/145) in a vegetative or totally dependent state (3% GOS-E 2,  
24 15% GOS-E 3), and 28% of patients being dead (N=41/145; GOS-E 1). FUNC score

1 reliably predicted functional independence (GOS-E  $\geq 4$ ) at month 3 (32% (N=6/19) with  
2 a FUNC score  $\geq 9$  vs 3% (N=1/30) for those with a FUNC score of  $< 9$ ; p-value = 0.01).  
3 Patients that were unconscious at the time of MRI but predicted to be conscious at ICU  
4 discharge based on our model, more frequently were observed conscious at any time in  
5 the 30 days following the MRI (54% [N=22/41] vs 33% [N=4/12]; p-value = 0.3) and had  
6 better 3-month functional outcomes than those that were predicted to still be  
7 unconscious at discharge (GOS-E  $\geq 4$ : 35% (N=13/37) vs 0% (N=0/12) vs; p-value  
8 =0.02; Figure 4).

## 9 Discussion

10 More than half of ICH patients that are unconscious on admission are dead at one year  
11 after the bleed, and even though our ability to accurately prognosticate recovery is  
12 dismal, the primary mode of death is withdrawal of life sustaining therapies [24].  
13 Accurate prediction of functional outcomes is challenging in the acute setting and  
14 confounded by biases contributing to the self-fulfilling prophecy of poor outcomes  
15 [25,26]. In this study we show that lesions identified on MRIs obtained within one week  
16 of ICH not only correlate with level of consciousness at the time of MRI but, more  
17 importantly, are able to identify patients that will recover consciousness prior to ICU  
18 discharge and have better 3-month functional outcomes. The identified predictors  
19 confirm previous findings (ICH volume, MLS and IVH) but also provide new insight on  
20 subcortical structures implicated in the physiology of consciousness [1–7,12].

21 We confirm that measures reflecting the impact on both hemispheres (i.e., ICH  
22 and oedema volumes, MLS and IVH) are major determinants of impairment and  
23 recovery of consciousness, survival and functional outcomes. ICH volume is a well-

1 known prognostic factor for both 30-day mortality and 90-day disability [15,16]. MLS is  
2 linked to high ICH and oedema volume and is clinically associated with herniation. Both  
3 large ICH volumes and MLS are seen in patients with increased intracranial pressure.  
4 All of these variables may cause bilateral impairment of widespread brain regions,  
5 which frequently is associated with unconsciousness [2].

6 Additionally, we identified three main subcortical structures implicated with  
7 consciousness impairment. These findings further support the role of the pontine  
8 tegmentum and midbrain peduncles, which have been implicated reliably in several  
9 clinical studies [1–3,7]. Interestingly, the caudate nucleus, which has been implicated in  
10 wakefulness in the rat [27], is also included in many models of human consciousness as  
11 part of the frontal cortical–striatopallidal–thalamocortial loop systems [2,4,6]. According  
12 to the mesocircuit theory, a decrease in the indirect excitatory activity of the Medium  
13 Spiny Neurons of the caudate and the putamen nuclei (special type of GABAergic  
14 inhibitory neurons) on the thalamus could explain an alteration of consciousness [6].  
15 Hypometabolism of the caudate has been reported in unconscious patients [28] and, the  
16 caudate nucleus atrophies in chronic disorders of consciousness [8,29,30]. Reports of  
17 isolated bilateral caudate lesions are very rare but have been seen in patients with  
18 impairment of consciousness ranging from disorientation and confabulations to  
19 somnolence [31,32]. Caudate ICH has been previously associated with impairment of  
20 consciousness, however, since the caudate nucleus forms the wall of the lateral  
21 ventricle, it frequently is associated with IVH, hampered causal inference [33]. In our  
22 study, the majority of the patients with caudate lesions also had IVH. However, these  
23 patients were less likely to be conscious, both at time of MRI and ICU discharge, than

1 patients with IVH in the absence of a caudate lesion (see supplementary material). At a  
2 minimum, caudate lesions appear to play a mediating effect on the relationship between  
3 IVH and impairment of consciousness. Finally, it is worth noting that the weights  
4 attributed to caudate lesions were systematically greater than for IVH. In light of these  
5 findings, the present study provides further support implicating lesions of the caudate  
6 nucleus in impairment and early recovery of consciousness, independently from the  
7 frequently associated IVH.

8 The patient cohort studied here is not necessarily representative for all ICH  
9 patients as our enrolment bias analysis illustrates. Patients that were included tended to  
10 have slightly less neurological impairment, smaller haemorrhages, amyloid aetiology,  
11 and better outcomes. This is likely a reflection of provider safety concerns for MRI  
12 scanning and family preferences.

13 This study has several limitations. First, assessment of consciousness relied on a  
14 previously described, standardized neurological assessment [17] instead of a scale  
15 specifically developed for the assessment of consciousness such as the Coma  
16 Recovery Scale Revised (CRS-R) [34]. However, the CRS-R has some limitations in the  
17 ICU setting as it was primarily developed for patients in the subacute and chronic  
18 rehabilitation setting. Assessments with the CRS-R are time consuming posing a  
19 challenge in a hectic ICU environment during which patients consciousness level often  
20 fluctuates. We acknowledge that this assessment of consciousness will likely  
21 underestimate the presence of conscious and does not capture patients with cognitive  
22 motor dissociation [35,36]. Second, assessments of consciousness in patients with  
23 aphasia and delirium may be challenging. To capture nonverbal command following in

1 aphasic patients we assessed, both verbal and non-verbal (i.e. mimicking) commands.  
2 Delirium in general and hypoactive delirium in particular are common in acutely brain  
3 injured patients and can interact with consciousness assessments. This confounder will  
4 affect any behavioural assessment in brain injured patients including the CRS-R [37].  
5 However, the vast majority of patients with hyperactive delirium would be expected to  
6 demonstrate at least intermittent command following. Third, sedation is frequently used  
7 in the critical care setting and can confound assessments of consciousness. We  
8 minimized doses of sedation as recommended in guidelines [38] and systematically  
9 accounted for sedation given at the time of and preceding the assessment at time of  
10 MRI. Note that this limitation only applies the model trained at time of MRI since none of  
11 the patients received sedation at time of ICU discharge. Fourth, MRI based  
12 assessments of haemorrhage can be challenging as MRI signal changes are observed  
13 over time [39]. Subacute haemorrhages typically appear as hypointense signal in FLAIR  
14 sequences between 2-7 days, which was within the inclusion criterion in this study.  
15 Finally, confirmatory investigations to validate our findings on an independent dataset  
16 will be necessary in future studies.

17 Taken together, our results suggest that measures of injury obtained from routine  
18 clinical MRI sequences may allow to predict failure to recover consciousness by ICU  
19 discharge and functional outcomes in patients with acute brain injury more accurately.  
20 Focal lesions in key structures within previously described models of consciousness  
21 together with measures related to mass effect of the haemorrhage predict early  
22 recovery of consciousness. Both, adding a comprehensive assessment of structural  
23 connectivity between these key structures (i.e., using diffusion tensor imaging analysis)

- 1 [40] as well as quantifying functional connectivity (using functional imaging or EEG
- 2 markers) may further strengthen the accuracy of this model.

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9 data.

## 1 Tables

2 **Table 1.** Baseline characteristics of the reported cohort and enrolment bias.

	<b>MRI (N=158)</b>	<b>No MRI (N=532)</b>	<b>p-value</b>
Age, years	68 [54, 77]	63 [50, 76]	0.05
Female	71 (45)	244 (47)	0.6
White	51 (32)	148 (29)	0.4
Presumed aetiology			< 0.01
Hypertensive	78 (49)	241 (48)	
Amyloid	59 (37)	62 (12)	
Coagulopathy*	16 (10)	86 (17)	
Other	5 (3)	121 (24)	
GCS at admission	14 [9,15]	10 [5, 15]	< 0.01
<b>ICH characteristics on admission CT</b>			
Lobar	56 (35)	110 (21)	< 0.01
Deep	62 (39)	240 (47)	0.1
Infratentorial	28 (18)	-	-
ICH vol			< 0.01
<30	121 (78)	306 (66)	
30-60	27 (17)	89 (19)	
>60	7 (5)	69 (15)	
IVH	72 (47)	281 (59)**	< 0.01
<b>ICH prognostic scores</b>			
ICH score	1[1, 2]	2 [1, 3]	< 0.01
FUNC score	9[7, 10]	8 [6, 9]	< 0.01
<b>Hospital course</b>			
EVD	31 (20)	142 (27)	0.05
Clot evacuation	16 (10)	69 (13)	0.3
ICU stay, days	4 [2, 8]	-	
Hospital stay, days	10 [6, 20]	-	
<b>Outcome 3 months</b>			
GOS	3 [2, 4]	3 [2, 5]	< 0.01
GOS-E	4 [1, 6]	-	
Dead	24 (22)	158 (42)**	< 0.01

3  
4 Data reported as n (%) or median [25%-IQR, 75%-IQR] as appropriate.  
5 MRI: Magnetic Resonance Imaging; GCS: Glasgow Coma Scale; ICH: Intracerebral  
6 Haemorrhage; CT: Computed Tomography; IVH: Intraventricular Haemorrhage; EVD:  
7 External Ventricular Drain; ICU: Intensive Care Unit; GOS: Glasgow Outcome Scale;  
8 GOS-E: Glasgow Outcome Scale – Extended. \* Coagulopathy, primary haematological  
9 disorder and medication induced combined; \*\* more than 5% missing data.

1 **Table 2.** Weights of models predicting consciousness at time of MRI and at time of ICU  
2 discharge.

Subcortical ROIs	Conscious at time of MRI		Conscious at time of ICU discharge	
	ICH	Oedema	ICH	Oedema
Caudate ipsi	<b>-0.12[-0.7, 0]</b>	<b>-0.32[-0.65, 0]</b>	<b>-0.78[-1.14, -0.25]</b>	<b>-0.72[-0.99, -0.48]</b>
Caudate contra	0[0, 0]	0[0, 0]	0[0, 0]	0[0, 0]
Putamen ipsi	0[0, 0]	0[0, 0]	0[0, 0]	0[0, 0]
Putamen contra	<b>0[-0.03, 0]</b>	<b>0[-0.32, 0]</b>	0[0, 0]	0[0, 0]
Pallidum ipsi	0[0, 0]	<b>0.31[0, 0.72]</b>	0[0, 0]	0[0, 0]
Pallidum contra	<b>0[0, 0.67]</b>	<b>0[-0.82, 0]</b>	0[0, 0]	0[0, 0]
Thalamus ipsi	<b>0[-0.06, 0]</b>	0[0, 0]	0[0, 0]	0[0, 0]
Thalamus contra	0[0, 0]	0[0, 0]	0[0, 0]	0[0, 0]
Basal forebrain	0[0, 0]	0[0, 0]	0[0, 0]	<b>0[0, 0.42]</b>
Hypothalamus	0[0, 0]	<b>0[-0.06, 0]</b>	0[0, 0]	0[0, 0]
Midbrain peduncule ipsi	0[0, 0]	0[0, 0]	<b>0[-0.12, 0]</b>	0[0, 0]
Midbrain peduncule contra	0[0, 0]	<b>-1.05[-1.75, 0]</b>	0[0, 0]	<b>0[0, 0.73]</b>
Central midbrain	<b>0.6[0, 1.97]</b>	0[0, 0]	0[0, 0]	0[0, 0]
Pontine tegmentum	0[0, 0]	<b>-0.05[-1.2, 4 0]</b>	0[0, 0]	<b>-0.86[-1.59 -0.21]</b>
<b>Diffuse injuries*</b>				
Volume	<b>-3.57[-4.9, -1.92]</b>	<b>-0.94[-1.74, -0.01]</b>	<b>-3.5[-4.53 -2.7]</b>	<b>-0.87[-1.54, -0.34]</b>
MLS	<b>-2.94[-4.41, -1.64]</b>		<b>-1.12[-1.75, 0.51]</b>	
IVH	0[0, 0]		<b>-0.58[-0.79, -0.41]</b>	

3  
4 Data given as median [25%-IQR, 75%-IQR] of the weights obtained over the 500 cross  
5 validation iterations. Negative values indicate prediction of being unconscious, positive  
6 values of being conscious.

7 ROI: Region of Interest; ipsi: ipsilateral; contra: contralateral; MLS: Midline shift; ICH:  
8 Intracerebral Haemorrhage; IVH: Intraventricular Haemorrhage. \*: Volume weights  
9 correspond to 10ml units, MLS weights correspond to 1mm changes and IVH was  
10 dichotomized as present or absent.