Brain regions important for recovery after severe post-stroke upper limb paresis

Jane M Rondina,1 Chang-hyun Park,2 Nick S Ward1,3,4

ABSTRACT

Background The ability to predict outcome after stroke is clinically important for planning treatment and for stratification in restorative clinical trials. In relation to the upper limbs, the main predictor of outcome is initial severity, with patients who present with mild to moderate impairment regaining about 70% of their initial impairment by 3 months post-stroke. However, in those with severe presentations, this proportional recovery applies in only about half, with the other half experiencing poor recovery. The reasons for this failure to recover are not established although the extent of corticospinal tract damage is suggested to be a contributory factor. In this study, we investigated 30 patients with chronic stroke who had presented with severe upper limb impairment and asked whether it was possible to differentiate those with a subsequent good or poor recovery of the upper limb based solely on a T1-weighted structural brain scan.

Methods A support vector machine approach using voxel-wise lesion likelihood values was used to show that it was possible to classify patients as good or poor recoverers with variable accuracy depending on which brain regions were used to perform the classification.

Results While considering damage within a corticospinal tract mask resulted in 73% classification accuracy, using other (non-corticospinal tract) motor areas provided 87% accuracy, and combining both resulted in 90% accuracy.

Conclusion This proof of concept approach highlights the relative importance of different anatomical structures in supporting post-stroke upper limb motor recovery and points towards methodologies that might be used to stratify patients in future restorative clinical trials.

INTRODUCTION

Stroke is one of the the most common causes of physical disability worldwide and about 80% of stroke survivors experience impairment of movement on one side of the body.1 Hand and arm impairment in particular is often persistent, disabling and a major contributor to reduced quality of life.2 The main predictor of long-term outcome of upper limb function is the level of initial impairment.3 This can be quantified as the proportional recovery rule which states that by 3 months, patients with stroke will recover about 70% of the initial upper limb motor impairment that has been observed on day 3 post-stroke.4-6 The prediction works extremely well for those presenting with mild to moderate upper limb impairment, but in only about half of those with initially severe upper limb impairment.4,6 In the other half, patients do worse than predicted, that is, there is a failure of proportional recovery. A key question then is, what is the difference between patients with stroke matched for initial severity who go on and have different recovery trajectories? The answer to this will point to the factors that are important for the dynamic process of recovery independent from the causes of initial impairment.

One possibility is the anatomy of the damage may be different in each group. A number of recent studies have proposed that the corticospinal tract (CST) plays a decisive role in this categorical difference7-11 as cortical reorganisation for improved motor function ultimately requires access for cortical motor areas to muscles. However, CST lesion load correlates with initial motor impairment,12 which is the major predictor of long-term outcome. It is therefore reasonable to ask how much CST lesion load can improve prediction of long-term outcome over and above initial severity. Furthermore, most of the patients involved in these studies had suffered from subcortical stroke and recent work has suggested that taking account of cortical damage after stroke can improve prediction of the motor clinical consequences.13 14

In this study, we investigated 30 patients with chronic stroke with a range of lesion locations (cortical and/or subcortical involvement) known to have presented with severe initial upper limb impairment but who had gone on to have quite different recovery trajectories. We applied a support vector machine approach to data representing lesion likelihood derived from structural T1-weighted MRI to answer the following questions. First, how accurately can patients with stroke with severe initial upper limb impairment be classified as having either good or poor recovery using only data extracted from whole brain structural MRI? Second, which brain regions contribute most to the classification? The results have the potential to transform how prediction of long-term upper limb outcome after stroke is achieved in routine clinical practice in future. The ability to easily and accurately predict outcome with standard clinical neuroimaging would have important implications for planning of treatment but also for stratification in future trials of restorative therapies.15

METHODS

Experimental design

Patients with stroke provided full written consent to take part in this study in accordance with the Declaration of Helsinki. The study was approved by the Joint Ethics Committee of the Institute of Neurology, University College London (UCL) and
Motricity Index and Nine-Hole Peg Test.18 A single representa-

tion–normalisation approach20 modified to include an extra 

cerebrospinal fluid). The procedure uses the unified segmen-

tation to the mid-sagittal plane so that all scans presented lesion in 

Anatomical T1-weighted volumetric MRI high-resolution 

images were acquired using a 3T Allegra scanner (Siemens 

AG, Erlangen, Germany) with the following protocol: number 

of slices=176, slice thickness=1 mm, matrix size=224×256, 

in-plane resolution=1 mm×1 mm. The origin of each image was 

set at the anterior commissure. Images from patients that had 
injury predominantly in the left hemisphere were flipped in rela-
tion to the mid-sagittal plane so that all scans presented lesion in 
the right hemisphere.

Data representation—obtaining lesion likelihood images 

Images where each voxel contains a measure representing the 
probability of being part of injured tissue were derived from the 
T1-weighted volumetric MRI scans using an automatic method 
for detection of outlier voxels.15 This approach is based on the 
assumption that lesions are characterised as atypical voxels 
regarding expected brain tissues (grey matter, white matter and 
cerebrospinal fluid). The procedure uses the unified segmen-
tation–normalisation approach20 modified to include an extra 
tissue to account for the perturbation introduced by lesions. In 
the resultant image, each voxel is assigned a value between 0 and 
1 that represents its probability of being part of a lesion. We call 
this representation lesion likelihood.

It is important to note that the lesion likelihood is different 
from lesion load, another way of extracting data from struc-
tural images, which has been commonly used in studies that 
predict poststroke outcome.21-23 The lesion load is a summarised 
measure that represents the proportion of voxels in the brain 
(or within an anatomical structure) that are considered to be 
injured. Thus, it requires a procedure to delineate the lesion. 
Using lesion likelihood data is superior to lesion load data in 
predicting motor impairment after stroke, irrespective of the 
region of interest used.14

Figure 1 displays an example of lesion likelihood image. The 
CST mask (represented in red) is circled in the enlarged image 
on the right side to show that each voxel inside the mask corre-
sponds to a feature (as opposed to the lesion load, where a single 
value (or feature) would be extracted).

Machine learning classification 

One of the most common objectives of machine learning algo-
rithms is classification, which attempts to assign each input 
value to one of a given set of classes. Classification analysis has 
become increasingly popular in clinical research, with potential 
to contribute to diagnosis, prognosis and prediction of treat-
ment response. In brief, classification methods work as follows: 
given a set of training examples, each one known to belong to a 
specific category (class), the training algorithm learns a func-
tion based on the values of each variable (feature). The decision 
function learnt from the training set is used to classify a new 
example (ie, to predict the category to which it belongs) based 
on the values of its variables. In neuroimaging, features usually 
correspond to voxels derived from a brain scan or some form of 
summarisation of groups of voxels.

Using lesion likelihood data as input features, we classified 
patients as good recoverers (GR) or poor recoverers (PR) by 
applying linear Support Vector Machine (SVM)26 implemented 
in LIBSVM library27 used in Pattern Recognition for Neuroim-
ing ToolBox.28 The problem of obtaining a decision function in 
SVM consists in finding a hyperplane (a plane in a hyper-
space), which has the largest margin between the closest exam-

ples across classes (called support vectors). When data from a 
new patient (not used to train the machine) is applied to the 
function, the class to which it belongs is determined.

Figure 2 presents a simplified representation of SVM to clas-
sify examples (patients) based on features (voxels from brain
images). In the simplification, we represented each example with two features only (e.g., one voxel corresponding to each hemisphere) to be able to illustrate it in a two-dimensional graph.

In our context, we have a binary classification (two classes, corresponding to GR and PR patients). The number of examples (n) is 30 and the number of features (p) corresponds to

the number of voxels in the analysis. Given the training data \((x_i, y_i)\) for \(i = 1 \ldots n\), with \(y_i \in \{-1, 1\}\), a classifier \(f(x)\) is learnt such that:

\[
f(x) = \begin{cases} 
-1, & x < 0 \\
1, & x \geq 0 
\end{cases}
\]
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A linear classifier has the form: \( f(x) = w^T x + b \), where \( w \) is known as the weight vector and \( b \) is a bias. Considering only two features, the discriminant function \( f(x) \) would be a line, as illustrated in figure 2. In a real analysis, however, each feature vector may contain thousands of voxels, thus being represented in a hyperspace.

The weight vector is a linear combination of the support vectors. A weight is assigned to each voxel, with larger weights indicating voxels of higher relevance for obtaining the discriminant hyperplane. Considering that a positive and a negative label are associated to each group (ie, \(+1= \) poor recoverers; \(-1= \) good recoverers), a positive weight assigned to a voxel means a higher relative level of lesion likelihood in that voxel for poor recoverers compared with good recoverers in the support vectors, and a negative weight means that lesion likelihood was higher for good recoverers. It should be noted that, as the weights are defined by the support vectors that are related to the placement of the discriminant hyperplane, both magnitude and the sign (positive or negative) of the weights are defined in a multivariate way and the discrimination is based on the complete pattern of voxels. Therefore, it is not appropriate to draw local inferences about particular voxels. Instead, weights of individual voxels should be interpreted within the context of their contribution to a wider discriminating pattern.

Delimiting regions of interest

To investigate the involvement of the CST and other ROIs, we defined binary masks to restrict voxels anatomically. A mask corresponding to the CST was obtained by probabilistic tractography from nine age-matched healthy volunteers in a previous study.29 Another mask was defined selecting a subset of ROIs from the Automated Anatomical Labeling (AAL) atlas30 that correspond to regions expected to be related to motor and sensorial function according to literature.31–34 The regions are the following (bilaterally): postcentral gyrus, precentral gyrus, supplementary motor area, superior frontal gyrus, middle frontal gyrus, inferior and superior parietal regions, thalamus, caudate, putamen and pallidum. We also performed a classification with a mask combining both the CST and the subset of the AAL ROIs selected. It is important to note that there was an intersection of 1128 voxels between the CST and the AAL ROIs selected. These voxels were removed from the motor ROIs mask, so that the both masks are disjoint.

### Table 1: Demographic and clinical characteristics of each group of patients: poor recoverers (PR) and (good recoverers (GR))

<table>
<thead>
<tr>
<th>Feature</th>
<th>PR n=15</th>
<th>GR n=15</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: mean (SD)</td>
<td>59.1 (7.2)</td>
<td>51.7 (10.8)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Gender, number of patients: M (F)</td>
<td>10 (5)</td>
<td>8 (7)</td>
<td>0.46**</td>
</tr>
<tr>
<td>Time since stroke: mean (SD) and range (months)</td>
<td>40.7 (42.6)</td>
<td>31.3 (28.2)</td>
<td>0.74*</td>
</tr>
<tr>
<td>Ratio of ischaemic to primary intracerebral haemorrhagic stroke</td>
<td>12.3</td>
<td>13.2</td>
<td>–</td>
</tr>
<tr>
<td>ARAT: mean (SD) (max 57)</td>
<td>32.9 (8.5)</td>
<td>52.7 (5.49)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Grip mean: (SD) (% unaffected side)</td>
<td>41.4 (14.3)</td>
<td>74.6 (18.57)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Motricity index: mean (SD) (% unaffected side)</td>
<td>65.2 (11.4)</td>
<td>91.9 (4.2)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>NHPT: mean (SD) (% unaffected side)</td>
<td>5.8 (5.9)</td>
<td>53.1 (23.7)</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

*\( p \) Value for Wilcoxon rank-sum test.
*\( * \) Value for \( \chi^2 \) test.

Results

Statistical analysis

To evaluate the generalisation ability of the model, the dataset was partitioned into training and testing sets using a ‘Leave-one-pair–out’ cross-validation approach, with one patient from each group left out for test at each iteration. The performance of the analysis was described through the percentage of true positives and true negatives (correctly classified PR and GR patients, respectively). Statistical significance was tested using permutation, a non-parametric approach through which the frequency distribution under the null hypothesis is obtained combining random rearrangements of the labels across the examples. As the correlation between examples and labels is destroyed, one expects the classification accuracy with permuted labels to be close to chance (around 50%). The number of permutations repeated in each analysis was 10,000 times.

### Table 2: Classification results

<table>
<thead>
<tr>
<th>Features delimitation</th>
<th>T(PR)</th>
<th>T(GR)</th>
<th>Acc</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain</td>
<td>73%</td>
<td>87%</td>
<td>80%</td>
<td>0.0102</td>
</tr>
<tr>
<td>CST mask</td>
<td>67%</td>
<td>80%</td>
<td>73%</td>
<td>0.0260</td>
</tr>
<tr>
<td>Motor ROIs mask</td>
<td>87%</td>
<td>87%</td>
<td>87%</td>
<td>0.0006</td>
</tr>
<tr>
<td>CST + Motor ROIs mask</td>
<td>87%</td>
<td>93%</td>
<td>90%</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Acc, accuracy (average between T(PR) and T(GR)); CST, corticospinal tract; p, statistical significance of the results (given by 10,000 permutations of the labels); ROI, region of interest; T(PR), proportion of poor recoverers correctly classified; T(GR), proportion of good recoverers correctly classified.

RESULTS

Thirty-eight patients with stroke with a SAFE score of 0 at presentation were found (from 150 patients) in the Sobell Stroke Database. When these patients were ranked according to their current upper limb motor score, we excluded the middle 20% (8 patients) to ensure clearly distinct recovery trajectories in our two groups. The remaining 30 patients (mean age 55.4 (SD 10.05) years, 12 females) were included in the analysis. Table 1 presents the description of demographic and clinical characteristics of each group. The continuous measures (age, time since stroke and the motor scales) were described through mean and standard variation for each group and the statistical difference between groups was tested using the Wilcoxon rank-sum test for each of these variables. The gender was described through the number of males and females, and the statistical significance between groups was tested using \( \chi^2 \). The lesion prevalence map for all patients is shown in online supplementary figure 1.
In the first analysis, we used all voxels in the whole brain (without applying masks to restrict anatomical ROIs). With this approach, it was possible to correctly classify 73% of the poor recoverers (true positive) and 87% of the good recoverers (true negative). Thus, the classification accuracy (average between true positive and true negative) was 80% (p=0.0102, given by permutation).

Restricting the voxels using the CST mask, 67% of the poor recoverers and 80% of the good recoverers were correctly classified (accuracy 73%, p=0.0260). Using the motor ROIs mask, 87% of the poor recoverers and 87% of the good recoverers were correctly classified (accuracy 87%, p=0.0006). The best result was obtained combining both masks (CST and motor ROIs), with 87% of the poor recoverers and 93% of the good recoverers correctly classified (accuracy 90%, p=0.0002) (table 2).

Figure 3 shows the discriminant maps for all analyses. The maps were obtained using the SVM weight vector averaged across all cross-validation folds and represent the relative relevance of each feature (voxel) to classify the groups. Although it is not possible to make inferences regarding the relevance of specific locations based on the weight vectors due to the multivariate nature of the analysis, it is observable that there are some aggregations of voxels of similar weights (both positive and negative) and that the patterns of weights differ between left and right hemispheres in all analysis.

DISCUSSION

We have used a support vector machine approach to classify patients with stroke presenting with severe upper limb motor impairment as good or poor recoverers using only structural brain images containing voxel-wise information about the probability of damage. There are three key findings: (1) Classifying patients with stroke good or poor recoverers using only information from structural brain images is feasible; (2) Accurate classification was possible when using lesion likelihood information from just the CST, supporting the idea that a lower level of CST injury is important for recovery independent of its effect on initial severity of motor impairment; (3) However, classification using only voxels within regions commonly associated with motor and sensory function led to a substantial improvement in the classification accuracy in comparison with both the whole brain and the CST only models. This proof of concept approach highlights the relative importance of different anatomical structures in supporting upper limb motor recovery after stroke over and above their effect on initial impairment.

The proportional recovery rule principally demonstrates that the most important predictor of long-term upper limb outcome is initial severity. However, the presence of non-fitters to this rule indicates that other factors are important for understanding the dynamic process of recovery of motor function. We have not sought to replicate the proportional recovery result but have simply exploited the finding that patients presenting with severe impairment can have quite different recovery patterns (at the impairment level). This has allowed us to examine the anatomical factors important for upper limb motor recovery independent of their effects on initial severity. Previous hypotheses concerning why some patients fail to achieve good recovery have focused on the anatomy of the damage, in particular CST damage. Because CST damage correlates with initial upper limb severity and because many of the patients previously studied did not have cortical damage, we have extended these findings to include consideration of damage to cortical regions, and in particular, sensorimotor-related cortical regions. Our results highlight the relative importance of quantifying damage in these non-CST motor-related regions and argue for their inclusion to be tested in future predictive models for long-term upper limb outcome.

The proportional recovery rule has to date used the upper limb Fugl-Meyer scale. However, we did not have access to initial upper limb Fugl-Meyer scores, and so the results are not directly comparable to those previous studies. However, here we were not seeking to replicate the proportional recovery rule, but rather investigate why some patients who present with severe upper limb impairment recover and why some fail to recover, given that this difference could not be explained by initial severity. The patients in this study all had severe upper limb impairment according to a SAFE score of 0.10 It should be noted that the SAFE score has been obtained retrospectively. However, rather than relying on patient recall, the MRC grading scale score for SA and FE was recorded in the medical notes at the time of assessment in all cases and so is likely to be accurate.
Movement disorders

In relation to the outcomes in the chronic stage, inspection of the mean scores demonstrates our key requirement, namely that patients in each group have very different recovery trajectories. Despite not using the Fugl-Meyer score, our cohort represents a group of patients with stroke with severe upper limb impairment at 72 hours poststroke, who then separate into those with good recovery and those with poor recovery. As such, our results are still relevant for examining the residual structural brain architecture that supports upper limb recovery.

An important advantage of using patterns of voxels representing lesion likelihood instead of quantifying the lesion load is that the patterns take into account how the lesion spreads throughout anatomical regions, while lesion load presents a single value representing the proportion of damage in an anatomical structure. The same lesion load distributed according to different patterns can lead to different outcomes, especially in structures such as the CST that is particularly directional due to the tracts of fibres. Another advantage of using data represented as lesion likelihood is that there is no need to actually segment the lesions, avoiding a potential bias caused by threshold to obtain binary images of lesions.

Our findings support previous studies based on other methods that propose the important role of the CST as a biomarker for predicting recovery. Using less than 1% of the voxels of the whole brain, it was possible to classify good and poor recoverers with accuracy of 73%. However, the inclusion of other brain regions believed to be involved in reorganisation of motor functions led to an increase of the classification accuracy to 90%, suggesting that the information regarding the integrity of other cortical and subcortical areas potentially involved in sensorimotor function can also be important to predict recovery in patients who are severely impaired. It is also noticeable that the classification using the motor ROIs (excluding any intersection with the CST mask) resulted in better accuracy than using the CST itself.

There was a significant difference in age between our groups. The mean age of the poor recovery group was 7.4 years older than the good recovery group, although overall the average age was still below 60 and so this represents a relatively young stroke cohort. Increasing age confers a small risk of worse upper limb outcome overall, but age has not been reported to be a factor important for proportional recovery. Further evidence demonstrates that old patients benefit from high-intensity rehabilitation following stroke to the same degree as younger patients. It therefore remains to be seen whether this result holds true in a larger prospective cohort.

Our findings support the principle that accurate prediction of upper limb outcome using clinically acquired brain imaging data is a feasible and achievable goal in future. Our analysis relies only on automatic procedures and on structural T1-weighted MRI, an imaging protocol that is commonly acquired in clinical routine after stroke. This study is retrospective and requires further investigation in prospective studies with imaging data collected early after stroke. We will test whether the successful results obtained in the classification of different recovery trajectories of patients presenting with severe upper limb impairment (SAFE score=0) can be replicated in a longitudinal study, so that predictions early after stroke can contribute to more effective triage and stratification for neurorehabilitation. Beyond this however, the development of accurate models to predict functional outcomes after stroke is an important clinical priority. This work, together with work in different domains such as language, indicates that simple structural brain imaging together with automated analysis procedures can play an important role. Accurate predictive models will be important for planning of treatment but also for stratification in future trials of restorative therapies.

Contributors JMR contributed to the study planning, conducted the analyses, elaborated the tables and figures and wrote the first draft of the manuscript. NSW collected the data, planned the study, interpreted the results and contributed to the manuscript writing. ChP preprocessed the images and contributed to the manuscript writing. All authors reviewed the manuscript.

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