Is there full or proportional somatosensory recovery in the upper limb after stroke? Investigating behavioral outcome and neural correlates

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**Background:** Proportional motor recovery in the upper limb has been investigated, indicating about 70% of the potential for recovery of motor impairment within the first months post stroke. **Objective:** To investigate whether the proportional recovery rule is applicable for upper limb somatosensory impairment, and to study underlying neural correlates of impairment and outcome at six months. **Methods:** A total of 32 patients were evaluated at 4-7 days and six months using the Erasmus MC modification of the revised Nottingham sensory assessment for impairment of (1) somatosensory perception (exteroception) and (2) passive somatosensory processing (sharp/blunt discrimination and proprioception); (3) active somatosensory processing was evaluated using the stereognosis component of the Nottingham sensory assessment. MRI scans were obtained within one week post stroke from which lesion load was calculated for key somatosensory tracts. **Results:** Somatosensory perception fully recovered within six months. Passive and active somatosensory processing showed proportional recovery of 86% (95%CI: 79%-93%) and 69% (95%CI: 49%-89%), respectively. Patients with somatosensory impairment at 4-7 days showed significantly greater thalamocortical and insulo-opercular tract lesion load (p<0.05) in comparison to patients without impairment. Sensorimotor tract disruption at 4-7 days did not provide significant contribution above somatosensory processing score at 4-7 days, when predicting somatosensory processing outcome at six months. **Conclusions:** Our sample of stroke patients assessed early showed full somatosensory perception, but proportional passive and active somatosensory processing recovery. Disruption of both the thalamocortical and insulo-opercular tract early after stroke appears a factor associated with somatosensory impairment but not outcome.
Introduction

Upper limb motor function is frequently impaired after stroke, and displays a wide range of recovery from a complete flaccid and non-functional upper limb to (nearly) normal function[1]. Early prediction of recovery is clinically relevant to steer goal-setting and treatment selection[2], and can be useful to guide recruitment for clinical trials in the early phase[3]. Initial motor impairment, assessed by clinical scales such as the Fugl-Meyer Upper Extremity assessment (FM-UE), is considered a key predictor of motor recovery, as shown in several review studies concerning post stroke prognosis[4, 5]. More recently, the concept of proportional recovery has been introduced, demonstrating that after removing a subpopulation of patients with severe motor impairment and poor to none recovery (typically called ‘nonfitters’), in the remaining population (‘fitters’) a strong proportional relation exists between initial impairment and recovery[6-12]. In one of the first studies on this topic, Prabhakaran et al.[6] collected FM-UE at 24 to 72 hours and again at 3 months post stroke. For the sample excluding patients with severe initial impairment, they found that patients at 3 months obtained about 70% (95%CI: 57%-80%) of their maximal potential recovery, defined as the difference between the initial FM-UE score and the maximum score (66) of the scale[6].

Recent studies have investigated neural correlates underlying the proportional recovery rule with a focus on corticospinal tract integrity[3, 8, 12, 13]. Early neuroimaging and neurophysiology biomarkers have been found, such as fractional anisotropy (FA) asymmetry index at the level of the posterior limb of internal capsule (PLIC) and motor-evoked potentials (MEP) responses to transcranial magnetic stimulation (TMS). A recent large cohort study[3] confirmed the earlier study of Byblow et al.[8] by showing that patients with MEP responses to TMS will recover proportionally regardless of baseline impairment, whereas patients without MEP responses are expected to have limited to none recovery.

Further studies have confirmed the proportional recovery rule[3, 7] and investigated the applicability in other domains besides upper limb motor outcome, such as visuospatial neglect[9, 11] and aphasia[11, 14], suggesting a common underlying recovery paradigm,
which applies to motor and cognitive functions[11]. Finally, Smith and colleagues investigated proportional recovery from lower limb motor impairment by lower limb Fugl-Meyer assessments at 3 days and 3 months[10]. Their results showed proportional recovery of 74% (95%CI: 60%-88%) from lower limb impairment. Interestingly, there was no identifiable nonfitters group, i.e. patients who did not fit the proportional recovery rule[10].

A common deficit in the upper limb besides motor impairment is a somatosensory deficit. Meyer *et al.* investigated the prevalence of disorders in somatosensory modalities in the first 4 to 7 days post stroke and reported impairment in somatosensory modalities in 78% of patients[15]. Recent studies focusing on this topic showed that somatosensory deficits have significant relations with uni- and bimanual upper limb motor impairment and recovery[16,17]. So the question is whether the proportional recovery rule is applicable for somatosensory impairment. Therefore, we investigated patients at 4 to 7 days and 6 months after stroke and determined whether there is full or proportional somatosensory recovery. We analyzed the different components of somatosensory impairment: (1) somatosensory perception, defined as the ability to perceive a somatosensory stimulus (e.g. touch, pressure); (2) passive somatosensory processing, defined as the ability to discriminate between somatosensory stimuli (e.g. sharp/blunt discrimination, proprioception); and (3) active somatosensory processing (e.g. stereognosis), defined as the ability to recognize an object by the integration of somatosensory functioning and active manipulation. We hypothesized, based on earlier longitudinal work from our group[15], that there is full somatosensory perception recovery, but proportional passive and active somatosensory processing recovery. As we obtained magnetic resonance imaging from our patients, we were further able to test the hypothesis that somatosensory impairment would be shown in patients with disruption of sensorimotor pathways, and that the amount of disruption would relate to somatosensory outcome at six months.

**Methods**
For the present study, 38 consecutive patients were included from a previous study recruiting from the acute stroke unit of the University Hospitals Leuven (Belgium) and Cliniques Universitaires Saint-Luc, Brussels (Belgium) between October 2012 and September 2014[15]. Six patients did not complete the assessment at 6 months and were therefore excluded from the analysis. Inclusion criteria were: first-ever stroke (ischemic or hemorrhagic); assessment within the first week after stroke onset; presence of somatosensory and/or motor impairment, as detected by the Erasmus MC modification of the revised Nottingham sensory assessment (Em-NSA)[18] and Fugl-Meyer Upper Extremity assessment (FM-UE)[19]; and sufficient cooperation to perform the assessment. Subjects were excluded if presenting a pre-stroke Barthel Index[20] score <95 out of 100; other serious neurological conditions with permanent damage such as subdural hematoma, tumor, encephalitis or trauma that leads to similar symptoms as a stroke; serious communication, cognitive or language deficits, which could interfere with the assessment protocol. Ethical approval was obtained from the Ethics Committee of both University Hospitals. Written informed consent was signed prior to participation.

**Clinical assessment**

Subjects were evaluated by one trained research therapist (SM). Assessments were performed within the first week (between day 4 and 7 post stroke) and at 6 months after stroke. At the first assessment, patient characteristics were collected including age, gender, hand dominance, time post stroke, stroke severity (National Institutes of Health Stroke Scale, NIHSS[21]), lateralization and type of stroke (ischemic or hemorrhagic).

The clinical evaluation comprised the FM-UE, Em-NSA and the stereognosis component of the Nottingham sensory assessment (NSA-stereognosis) for the upper limb, assessed at both time points. Clinical scales were selected according to established validity and reliability together with a balance between clinical utility and psychometric properties[22].
The FM-UE[19] assesses motor impairment as a whole for the upper extremity including shoulder, elbow, wrist and hand assessment, from reflex activity to voluntary activation. The total score for the FM-UE ranges between 0 and 66, with a higher score representing less upper limb motor impairment. Excellent reliability and validity has been reported for investigating motor impairment[19-21, 23].

Somatosensory impairment was assessed by the Em-NSA[18] in which five distinct somatosensory modalities in the affected upper limb are evaluated; light touch, pressure, pinprick, sharp-blunt discrimination and proprioception. Light touch is tested with cotton wool, pressure with the index finger, pinprick with a toothpick and sharp-blunt discrimination with alternating the index finger and a toothpick, all at predefined points of contact. Proprioception is assessed during passive movements of the different joints of the upper limb. Each site is assessed 3 times and graded in an ordinal scale as a zero (patient fails to detect sensation on all 3 occasions), 1 (identifies test sensation, but not on all 3 occasions) or 2 (correctly identifies the test sensation on all 3 occasions), and this is repeated over several sites in each modality. Scores for each modality range on a scale from zero (complete somatosensory impairment) to eight (no somatosensory impairment). The total score for the Em-NSA ranges from 0 to 40, with a higher score representing less upper limb somatosensory impairment. A score of less than 40 indicates somatosensory impairment[18, 24]. The Em-NSA has good to excellent intra-rater and inter-rater reliability[18] and validity[25], and is a recommended measure of sensation in neurological conditions[22]. Light touch, pressure and pinprick were grouped as measures of somatosensory perception. Sharp-blunt discrimination and proprioception were clustered as measures of passive somatosensory processing impairment.

Active somatosensory processing was evaluated through stereognosis which assesses the ability to identify an object by manipulation with eyes closed. Stereognosis assessment was based on the original NSA, in which participants are asked to identify 11 common objects by touch and manipulation in the affected hand. When needed, assistance to the manipulation of objects in the hand was given by the assessor. Total scores range from 0 to 22. A cut-off
score of less than 19 was used for the presence of stereognosis impairment[15]. The stereognosis section of the NSA shows a moderate to good test-retest reliability in people with stroke[26].

**Imaging acquisition, lesion segmentation and overlay, and probabilistic fiber tracking**

Together with being assessed clinically at the first assessment 4 to 7 days post stroke, our patients underwent an imaging protocol within the first week post stroke and subsequent imaging analysis was performed, as reported elsewhere[27]. Magnetic resonance images of the brain were obtained with a Philips 3T Achieve scanner. Either 3D or 2D fluid attenuated inversion recovering imaging (FLAIR) data and diffusion-weighted images (DWI) were acquired. Parameter settings for FLAIR sequences were: echo time = 350 ms, repetition time = 4800 ms, inversion time = 1650 ms, field of view = 250 × 250 mm², slice thickness = 1.12 mm, and gap = 0.56 mm. Parameter setting for DWI sequences were: number of slices = 58, number of gradient directions = 60, b-value = 1300 s/mm², echo time = 72 ms, repetition time = 12 s, slice thickness = 2.5 mm, gap = 2.5 mm.

Thalamocortical tract (TCT), insulo-opercular tract (IOT) and corticospinal tract (CST) probabilistic fiber tracking were obtained from DWI of 24 healthy, age-matched volunteers, as described elsewhere[27]. A 3T Siemens SkyraMRI scanner (Siemens, Erlangen, Germany) and 32-channel head coil were used. 75 axial slices were obtained covering the whole brain with gradients (b = 1500 s/mm²) applied along 64 non-collinear directions with the sequence parameters: Repetition time = 10,000 ms, echo time = 82 ms, field of view = 256 × 204, slice thickness = 2 mm, in-plane resolution = 2 × 2 mm². All datasets were corrected for eddy currents and head motion. Common somatosensory tracts were created using voxels that were found in at least 50% of the participants. Individual pyramidal tracts were also created analogously using the precentral cortex as seeding mask and waypoints in the posterior internal capsule (MNI coordinates z = 5 to z = 7), cerebral peduncle and pontomedullary junction (z = -44 to z = -48). Only streamlines starting from primary motor cortex and passing all three masks were kept. Further exclusion masks were used to avoid interhemispheric
trajectories, aberrant pathways and loops via subcortical or cerebellar structures. Default settings of the tracking algorithm (protrackx) were used (curvature threshold: 0.2; step length: 0.5mm; distance correction: off). The resulting VOIs were overlaid on lesion volumes to measure TCT, IOT and CST lesion load (TCT-LL%, IOT-LL% and CST-LL%, respectively), defined as the percentage of tract volume (voxel) which was within the volume of the stroke lesion [3].

**Statistical analysis**

Patient characteristics were analyzed and presented through descriptive statistics. Clinical scores of somatosensory perception, and passive and active somatosensory processing impairment obtained at 4 to 7 days and 6 months post stroke were used to calculate (1) potential recovery, defined as the difference between the score obtained at 4 to 7 days and the maximum score of the scale; and (2) observed recovery, defined as the difference between the scores obtained at 6 months and scores at 4 to 7 days. Subsequently, scatterplots were derived displaying potential and observed recovery. We applied the same analysis for motor impairment (FM-UE), as validation of our sample, expecting to find proportional motor recovery in line with previous literature. On the scatterplot of motor recovery, we identified visually a fitters and nonfitters group for proportional recovery and investigated the existence of these groups through agglomerative hierarchical clustering analysis (Ward’s Method, Squared Euclidean Distance). On the scatterplots of somatosensory perception and processing recovery, there was no nonfitters group identified through hierarchical clustering analysis. We noted one possible outlier for somatosensory perception and passive somatosensory processing; a patient with very severe somatosensory impairment and a poor somatosensory recovery. We applied a standard test for outliers (Standardized residuals), which confirmed this subject as an outlier and removed this subject from subsequent regression analysis. For clarity, we will refer to fitters/nonfitters grouping when discussing about motor recovery and to the whole group when discussing about somatosensory recovery.
Next, a univariate linear regression analysis was conducted for somatosensory recovery (whole group) and motor recovery (fitters) separately, with potential recovery included as explanatory variable and observed recovery as outcome variable. The resulting slope of the regression equation represents then the somatosensory and motor recovery model. Bootstrapping (single sampling method, 1000 samples, 95% CI) was performed to test the robustness of regression models.

Finally, to study neural correlates of somatosensory impairment, between-group differences for patients with normal and decreased somatosensory performance at 4-7 days were investigated for TCT-LL%, IOT-LL%, and CST-LL% obtained within one week post stroke using non-parametric tests (Mann Whitney U). For somatosensory domains that showed proportional recovery, a univariate and multivariate regression analysis was conducted, evaluating whether TCT-LL%, IOT-LL%, and CST-LL%, in combination with the clinical score at 4-7 days, contributed to predicting somatosensory outcome at six months. Level of significance was set at $p<0.05$. Analyses were performed using IBM SPSS Statistics for Windows, Version 24 (Armonk (NY), USA).

Results

In total, 32 patients were included in the present analysis. Median (IQR) age was 68 (61-80) years, 53% of patients were male and 84% had an ischemic stroke. Out of 32 patients, 23 (72%) had a right-sided lesion. All patients were evaluated at 4-7 days (median: 6, IQR: 5-7 days) and at 6 months (median: 183, IQR: 181-185 days) from stroke onset. Stroke severity, as evaluated by the NIHSS, showed a median of 8 (IQR: 5-13) out of 42 points. Upper limb somatosensory impairment, as assessed by Em-NSA showed median scores of 33 (IQR: 13-40) out of 40 at 4-7 days and 40 (IQR: 39-40) out of 40 at 6 months. Median upper limb motor impairment (FM-UE) was 20 (IQR: 2-55) out of 66 at 4-7 days and 59 (IQR: 10-64) out of 66 at 6 months. Our sample ranged from severely to mild impaired patients and further characteristics are provided in Table 1.
Scatterplots presenting potential and observed recovery are provided in Figure 1. For motor recovery (1A), nonfitters are indicated as grey triangles. Scatterplots for somatosensory perception, and active and passive somatosensory processing are presented in Figures 1B, 1C and 1D, respectively. For clarity, we highlighted the nonfitters group from the motor recovery scatterplot in the somatosensory scatterplots by means of the same grey triangles.

Table 2 presents the univariate linear regression analysis results for somatosensory and motor impairment. For fitters for motor recovery (n=23, 72%), the proportional recovery model for observed recovery showed a Beta coefficient of 0.68 (95% CI: 0.48-0.87) for potential recovery with an explained variance (adjusted $R^2$) of 70% ($p<0.001$) (Figure 1A). For the whole group for somatosensory perception, the model showed a Beta coefficient of 0.99 (95% CI: 0.96-1.01) with an explained variance of 99% (Figure 1B). For the whole group for passive somatosensory processing, the model showed a Beta coefficient of 0.86 (95% CI: 0.79-0.93) with an explained variance of 95% ($p<0.001$) (Figure 1C). And for the whole group for active somatosensory processing, the model showed a Beta coefficient of 0.69 (95% CI: 0.49-0.89) with an explained variance of 61% ($p<0.001$) (Figure 1D). Bootstrapping confirmed the robustness of regression models for passive somatosensory processing (SE=0.04, CI: 0.76-0.93, $p<0.01$), for active somatosensory processing (SE=0.09, CI: 0.51-0.86, $p<0.01$) and for motor recovery (SE=0.11, CI: 0.45-0.89, $p<0.01$). All y-intercepts were almost zero (-0.03 to 0.36).
Figure 2 presents the lesion overlay plots for our stroke sample (A), the thalamocortical, insulo-opercular and pyramidal tracts display in healthy volunteers (B1) as well as a three-dimensional visualization of these tracts (B2). Lesion load within sensorimotor tracts were compared between patients with normal and decreased somatosensory performance (Table 3). At 4-7 days, patients with impaired somatosensory perception showed significantly higher lesion load for all sensorimotor tracts ($p<0.00$) in comparison with patients without impairment. For passive and active somatosensory processing, impaired patients showed a significantly higher lesion load in the thalamocortical and insulo-opercular tract ($p<0.05$) compared to patients without dysfunction.

Univariate analysis for passive somatosensory processing at six months demonstrated a significant relation with passive somatosensory processing score at 4-7 days (adjusted $R^2=0.27; p=0.002$), TCT-LL% (adjusted $R^2=0.21; p=0.01$), IOT-LL% (adjusted $R^2=0.11; p=0.04$) and CST-LL% (adjusted $R^2=0.18; p=0.01$). When combining all variables in a multivariate analysis, only passive somatosensory processing score at 4-7 days was retained as significant variable. Univariate analysis for active somatosensory processing at six months demonstrated only a significant relation with active somatosensory processing score at 4-7 days (adjusted $R^2=0.23; p=0.003$). TCT-LL% (adjusted $R^2=0.05; p=0.13$), IOT-LL% (adjusted $R^2=0.00; p=0.31$) and CST-LL% (adjusted $R^2=0.03; p=0.18$) did not show a significant relation with active somatosensory outcome at six months.

Discussion

The aims of the present study were to assess whether the proportional recovery rule is also applicable for upper limb somatosensory impairment after stroke and whether neural correlates of somatosensory impairment and outcome could be identified. Results from data collected at 4-7 days and 6 months showed that there is full recovery for somatosensory
perception but proportional recovery for passive and active somatosensory processing. At 4-7 days, both the thalamocortical and insulo-opercular tract showed a greater lesion load in impaired patients compared to patients without somatosensory dysfunction for somatosensory perception, and passive and active somatosensory processing. A significant relation was demonstrated for sensorimotor tract disruption at 4-7 days and passive somatosensory processing outcome at six months, however there did not appear an additional explanatory value above the passive somatosensory processing score at 4-7 days, when entered in a multivariate model.

We included analysis of proportional recovery for upper limb motor impairment to demonstrate initial validity of our data. Indeed, our results confirm previous literature in this area as we found a proportional recovery of 68% (95% CI: 48%-87%). Again, as earlier identified, our study also showed that there is a group of patients presenting substantially less recovery than predicted (9/32=28%), and thus not following the proportional motor recovery model. In comparison, Winters and colleagues recognized a group of 65 out of 211 patients (31%) having substantially less recovery than predicted[7]. Thus, these results confirm the representative value of our sample to investigate upper limb somatosensory recovery.

We classified somatosensory modalities into three domains; somatosensory perception, and passive and active somatosensory processing. For somatosensory perception, i.e. the exteroceptive modalities, results showed essentially full recovery (99%, 95% CI including 1). Earlier results indeed showed that prevalence of the exteroceptive impairments in light touch, pressure and pinprick only existed in 6% or less of patients at six months after stroke[15].

For passive somatosensory processing, we observed proportional recovery (86%, 95% CI: 79%-93%). Passive somatosensory processing comprised sharp/blunt discrimination and proprioception. In earlier work [15], proprioceptive deficits only existed in 3% of patients at six months whereas sharp/blunt discrimination impairment was seen in 22% of the sample. Thus, our proportional recovery model could largely be steered by a sharp/blunt
discrimination deficit. Sharp/blunt discrimination and proprioception were grouped together as both require passive detection of somatosensory input and discrimination of this input (i.e. sharp or blunt stimulus, or position or movement sense in one or the other direction in case of proprioception). This is different from the exteroceptive modalities where only awareness of sensory input is required (i.e. is the touch, pressure or pinprick stimulus felt). In comparison to proportional recovery models for other domains, there is no nonfitter group identified although we recognized one outlier. Proportional recovery for passive somatosensory processing might indicate that a biological repair from a somatosensory impairment is reflected in a clinical change, although it should be noted that the level of proportional recovery (86%) is relatively higher in comparison to other domains. Confirmation of our findings is therefore required.

For active somatosensory processing, measured through stereognosis, we also observed proportional recovery (69%, 95% CI: 49%-89%). Stereognosis was classified as a different somatosensory domain as it requires detection of somatosensory input, discrimination as well as an active (motor) component when manipulating the objects in the hand. It should be noted that for patients in our sample who were unable to move the affected hand at all, the assessor passively moved the hand when testing stereognosis. The level of proportional recovery for active somatosensory processing (69%) is well in line with the reported rate of proportional recovery for visuospatial neglect[11], aphasia[11, 14] and lower limb motor impairment[10]. The proportional recovery for active somatosensory processing might (partly) be determined by the motor component required and thus by motor impairment recovery. Future research should attempt to disentangle the sensorimotor coupling in upper limb recovery after stroke.

Neural correlates of impairments in the different somatosensory domains at 4-7 days demonstrated that greater lesion load in the thalamocortical and insulo-opercular tracts were found in patients with impairment in comparison to patients without impairment. In earlier work using voxel-based symptom-mapping analysis[27], voxels with a significant association
to somatosensory impairments were grouped in two core brain regions; the sensory component of the superior thalamic radiation, and the parietal operculum close to the insular cortex. Further in our study, for patients with somatosensory perception impairment, a greater corticospinal tract lesion load was discovered compared to patients without impairment. This is somehow surprising, as in line with the argument raised above, one might expect a stronger relation between disruption of the corticospinal tract and active somatosensory processing, due to the latter requiring motor activity. However, other motor tracts such as the reticulospinal pathway might be more involved in the motor component of active somatosensory processing. As for the link between motor tract disruption and somatosensory perception impairment, this might be steered by the lesion sites and sizes in our sample and future studies should unravel this finding.

When relating somatosensory impairment and sensorimotor tract disruption early after stroke with sensorimotor outcome at six months, lesion load of the sensorimotor tracts was significantly related for passive sensorimotor processing only. No model was evaluated for somatosensory perception as there is essentially full recovery, with nearly-normal scores at six months. In multivariate models for passive and active somatosensory processing at six months, only the clinical processing score early after stroke was retained, with an explained variance of 23%-27%. This appears in line with motor prognostic models where imaging variables have limited predictive value. For proportional motor recovery models, imaging parameters have prognostic value determining non-fitters. However, we did not find non-fitter groups for proportional somatosensory processing recovery. The limited explained variance should encourage future research in understanding the early determinants of somatosensory outcome.

Some limitations of our study need to be considered. The sample size was limited; nevertheless, we obtained robust models, evaluated with bootstrapping analysis and our results confirmed previous literature concerning proportional motor recovery[3,6,7].
Nonetheless, the present results are based on recruitment from two centers in one country. Therefore future, large international cohort studies are needed to confirm proportional recovery model in the somatosensory domains, focusing on patients with somatosensory impairment as our sample included also participants without somatosensory deficit. Furthermore, we analyzed both ischemic and hemorrhagic stroke patients and recognize that previous studies included only ischemic patients. However Stinear et al.[3] recently generalized the proportional recovery model in a large cohort of both ischemic and hemorrhagic patients.

Conclusions

The present study is the first to demonstrate full recovery for upper limb somatosensory perception impairment but proportional recovery for passive and active somatosensory processing impairment in the upper limb after stroke. Patients with somatosensory impairment in the very early phase after stroke show greater lesion load in both the thalamocortical and insulo-opercular tracts. Disruption of sensorimotor tracts early after stroke was significantly related with passive somatosensory processing outcome at six months but does not appear to provide additional predictive value above passive somatosensory processing measured early.

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Conflict of interest

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References


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<th><strong>Table 1. Patient characteristics.</strong></th>
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<td><strong>Age stroke onset: years, median (IQR)</strong></td>
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<tr>
<td><strong>Gender, n (%)</strong></td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td><strong>Days after stroke, median (IQR)</strong></td>
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<tr>
<td>4-7 days</td>
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<td>6 months</td>
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<tr>
<td><strong>Affected hemisphere, n (%)</strong></td>
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<tr>
<td>Right</td>
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<tr>
<td><strong>Type of stroke, n (%)</strong></td>
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<tr>
<td>Ischemia</td>
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<tr>
<td>Hemorrhage</td>
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<td><strong>Hand dominance, n (%)</strong></td>
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<tr>
<td>Left</td>
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<tr>
<td>Right</td>
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<tr>
<td><strong>Stroke severity (NIHSS), median (IQR)</strong></td>
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<tr>
<td><strong>Em-NSA at 4-7 days, median (IQR)</strong></td>
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<td><strong>Em-NSA at 6 months, median (IQR)</strong></td>
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<tr>
<td><strong>Em-NSA somatosensory perception at 4-7 days, median (IQR)</strong></td>
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<td><strong>Em-NSA somatosensory perception at 6 months, median (IQR)</strong></td>
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<td><strong>Em-NSA passive somatosensory processing at 4-7 days, median (IQR)</strong></td>
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<td><strong>Em-NSA passive somatosensory processing at 6 months, median (IQR)</strong></td>
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<tr>
<td><strong>NSA-stereognosis (active somatosensory processing) at 4-7 days, median (IQR)</strong></td>
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<td><strong>NSA-stereognosis (active somatosensory processing) at 6 months, median (IQR)</strong></td>
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<td><strong>FM-UE at 4-7 days, median (IQR)</strong></td>
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<td><strong>FM-UE at 6 months, median (IQR)</strong></td>
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<td><strong>CST-LL% within one week, median (IQR)</strong></td>
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<td><strong>TCT-LL within one week, median (IQR)</strong></td>
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<td><strong>IOT-LL% within one week, median (IQR)</strong></td>
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NIHSS: National Institutes of Health Stroke Scale; Em-NSA: Erasmus MC modification of the (revised) Nottingham sensory assessment; NSA-stereognosis: stereognosis component of the Nottingham sensory assessment; FM-UE: Fugl-Meyer Upper Extremity assessment; TCT-LL%, IOT-LL% and CST-LL%: percentage (voxels) of the thalamocortical TCT), insulo-opercular (IOT) and corticospinal tract (CST) overlaid by the lesion.
Table 2. Univariate linear regression analysis results for somatosensory and motor impairment recovery models.

<table>
<thead>
<tr>
<th>Recovery model [clinical scale] (n, %)</th>
<th>B</th>
<th>SE B</th>
<th>95% CI</th>
<th>y-intercept</th>
<th>Adjusted $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatosensory perception [Em-NSA] (n=31, 97%)</td>
<td>.99</td>
<td>.01</td>
<td>.96 – 1.01</td>
<td>-0.03</td>
<td>.99*</td>
</tr>
<tr>
<td>Passive somatosensory processing [Em-NSA] (n=31, 97%)</td>
<td>.86</td>
<td>.03</td>
<td>.79 – .93</td>
<td>0.08</td>
<td>.95*</td>
</tr>
<tr>
<td>Active somatosensory processing [NSA-stereognosis] (n=32, 100%)</td>
<td>.69</td>
<td>.10</td>
<td>.49 – .89</td>
<td>0.22</td>
<td>.61*</td>
</tr>
<tr>
<td>Motor assessment [FM-UE] (n=23, 72%)</td>
<td>.68</td>
<td>.09</td>
<td>.48 – .87</td>
<td>0.36</td>
<td>.70*</td>
</tr>
</tbody>
</table>

Table 3. Comparison for thalamocortical, insulo-opercular and corticospinal tract lesion load between patients with impaired and normal somatosensory perception and processing.

<table>
<thead>
<tr>
<th>Domain (clinical scale)</th>
<th>Time post stroke</th>
<th>Group (n, %)</th>
<th>TCT-LL% 1W Median (IQR)</th>
<th>IOT-LL% 1W Median (IQR)</th>
<th>CST-LL% 1W Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatosensory perception (Em-NSA light touch, pressure and pinprick)</td>
<td>4-7D</td>
<td>Impaired (17, 57%)</td>
<td>16 (11-31)</td>
<td>54 (36-86)</td>
<td>15 (10-28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal (13, 43%)</td>
<td>1 (0-3)</td>
<td>0 (0-0.5)</td>
<td>4 (0-9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p</em>-value</td>
<td>.00</td>
<td>.00</td>
<td>.00</td>
</tr>
<tr>
<td>Passive somatosensory processing (Em-NSA sharp-blunt discrimination and proprioception)</td>
<td>4-7D</td>
<td>Impaired (19, 63%)</td>
<td>13 (4-26)</td>
<td>40 (1-83)</td>
<td>14 (4-19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal (11, 37%)</td>
<td>1 (0-4)</td>
<td>0 (0-10)</td>
<td>6 (0-19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p</em>-value</td>
<td>.00</td>
<td>.00</td>
<td>.14</td>
</tr>
<tr>
<td>Active somatosensory processing (NSA-stereognosis)</td>
<td>4-7D</td>
<td>Impaired (18, 60%)</td>
<td>12 (3-28)</td>
<td>38 (1-78)</td>
<td>11 (2-22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal (12, 40%)</td>
<td>2 (0-9)</td>
<td>0 (0-43)</td>
<td>11 (2-22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p</em>-value</td>
<td>.03</td>
<td>.03</td>
<td>.45</td>
</tr>
</tbody>
</table>

Em-NSA: Erasmus MC modification of the (revised) Nottingham sensory assessment; NSA-stereognosis: stereognosis component of the Nottingham sensory assessment; FM-UE: Fugl-Meyer Upper Extremity assessment; 4-7D: 4-7 days; 1W: within 1 week; TCT-LL%, IOT-LL% and CST-LL%: percentage (voxels) of the thalamocortical, insulo-opercular and corticospinal tract overlaid by the lesion, for the respective groups. Significant differences based on Mann Whitney U test are presented in bold.
Figure 1. Scatterplots for motor (A), somatosensory perception (B), passive somatosensory processing (C) and active somatosensory processing recovery (D).
FM-UE: Fugl-Meyer Upper Extremity assessment; Em-NSA: Erasmus MC modification of the (revised) Nottingham sensory assessment; NSA-stereognosis: stereognosis component of the Nottingham sensory assessment; potential recovery: difference between maximum score and the score obtained at 4-7 days; observed recovery: difference between the score obtained at 6 months and at 4-7 days. Black dots: fitters for motor recovery; grey triangles: nonfitters for motor recovery. For motor impairment, nonfitters were excluded from regression analysis; for somatosensory perception and passive somatosensory processing, one outlier was detected and excluded, which was also a nonfitter for motor recovery. Both hierarchical clustering and standardized residuals failed to detect any outliers or nonfitters group for active somatosensory processing impairment. Solid line: linear regression analysis; dotted line: linear regression for the whole group for the motor model.
Figure 2. Lesion overlay plot from stroke patients and DTI reconstruction for healthy subjects

A) Lesion overlay map of all patients

B1) DTI tracts in healthy volunteers

B2) 3D visualisation of DTI tracts
A. Individual lesion volumes were overlaid to show white matter regions most frequently involved. Maps are overlaid on a T1-template in MNI space $1 \times 1 \times 1 \text{ mm}^3$. All lesions were flipped to the left hemisphere. MNI coordinates of each transverse section (z-axis) and a sagittal slice for visualization are given. Color scale for lesion overlay indicates the number of patients presenting a lesion in this voxel. B1. Three different probabilistic fiber tracts of core sensorimotor brain pathways were taken from 24 healthy age-matched volunteers. Color scales for probabilistic fiber tracking indicates the number of volunteers presenting the tract in this voxel. B2. ‘Glass brain’ visualization and a half-split three-dimensional model of the three tracts is shown.