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Evidence of Motor Skill Learning in Acute Stroke Patients Without Lesions to the Thalamus and Internal Capsule

Audrey Riga, MSc; Estelle Gathy, MSc; Marisa Ghinet, MSc; Chloë De Laet, MSc; Benoît Bihin, PhD; Maxime Regnier, MSc; Maria Leeuwerck, MSc; Béatrice De Coene, MD; Laurence Dricot, PhD; Benoît Herman, PhD; Martin G. Edwards, PhD; Yves Vandermeeren, MD, PhD

BACKGROUND: It is currently unknown whether motor skill learning (MSkL) with the paretic upper limb is possible during the acute phase after stroke and whether lesion localization impacts MSkL. Here, we investigated MSkL in acute (1–7 days post) stroke patients compared with healthy individuals (HIs) and in relation to voxel-based lesion symptom mapping.

METHODS: Twenty patients with acute stroke and 35 HIs were trained over 3 consecutive days on a neurorehabilitation robot measuring speed, accuracy, and movement smoothness variables. Patients used their paretic upper limb and HI used their nondominant upper limb on an MSkL task involving a speed/accuracy trade-off. Generalization was evaluated on day 3. All patients underwent a 3-dimensional magnetic resonance imaging used for VSLM.

RESULTS: Most patients achieved MSkL demonstrated by day-to-day retention and generalization of the newly learned skill on day 3. When comparing raw speed/accuracy trade-off values, HI achieved larger MSkL than patients. However, relative speed/accuracy trade-off values showed no significant differences in MSkL between patients and HI on day 3. In patients, MSkL progression correlated with acute motor and cognitive impairments. The voxel-based lesion symptom mapping showed that acute vascular damage to the thalamus or the posterior limb of the internal capsule reduced MSkL.

CONCLUSIONS: Despite worse motor performance for acute stroke patients compared with HI, most patients were able to achieve MSkL with their paretic upper limb. Damage to the thalamus and posterior limb of the internal capsule, however, reduced MSkL. These data show that MSkL could be implemented into neurorehabilitation during the acute phase of stroke, particularly for patients without lesions to the thalamus and posterior limb of the internal capsule.

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Key Words: humans ■ internal capsule ■ motor skills ■ robotics ■ upper extremity

The first weeks after stroke are crucial for impairment recovery. Most studies quantifying the recovery of contralesional upper limb (UL) after stroke onset show that the most dramatic changes occur during the first 4 weeks.[1,2] Early after stroke, a cascade of biological processes occurs: reperfusion of the penumbral zone, edema resolution, inflammatory reactions, etc.[3–5] Interestingly, stroke triggers several intense and time-limited neural repair and plasticity processes, opening a transient critical window for recovery, which lasts for around 3 months.[6] While recovery may occur far beyond,[7] it seems logical to try to harvest the neuroplastic changes

Correspondence to: Yves Vandermeeren, MD, PhD, CHU UCL Namur, UCLouvain, Ave Dr Therasse 1, Yvoir 5530, Belgium. Email yves.vandermeeren@uclouvain.be
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Nonstandard Abbreviations and Acronyms

CMS	composite motor score
D1	first experimental day
D3	day 3
FMUE	Fugl-Meyer Upper Extremity Assessment
HI	healthy individual
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
MSkL	motor skill learning
PLIC	posterior limb of the internal capsule
SAT	speed/accuracy trade-off
SPARC	spectral arc length
UL	upper limb
VLSM	voxel-based lesion symptom mapping

unfolding early after stroke to maximize the interactions between spontaneous recovery (neural repair) and training-induced recovery (neurorehabilitation). Based on animal experiments, experts have proposed that the acute phase of stroke spans from 1 to 7 days after stroke onset, the early subacute phase from 7 days to 3 months, and the late subacute phase from 3 to 6 months.[6] Beyond 6 months poststroke, patients enter the chronic phase.

While the recovery from motor impairments has been extensively monitored from stroke onset to the chronic phase,[8,9] much less is known about the capacity to achieve motor skill learning (MSkL) during the acute phase of stroke. MSkL refers to the capacity to acquire and retain new sensorimotor skills such as lacing shoes or driving a car. MSkL is characterized by improvement of the speed/accuracy trade-off (SAT) and the ability to generalize learned skills to different contexts.[10,11] Improvement of SAT demonstrates that a skill is performed both faster and more accurately or that improvement in one component is not counterbalanced by a proportional deterioration in the other. MSkL is believed to be a key component for motor neurorehabilitation.[12,13]

The capacity to acquire and retain new motor skills during the acute phase of stroke is possible but underinvestigated. If motor learning rate remains normal, it is interesting at least to improve patient's independence for activities of daily life. Conversely, the capacity to achieve motor learning might be transiently depressed (or not possible) early after stroke, possibly caused by large biological perturbations and sensorimotor networks that have not yet been efficiently reconfigured. Since the physiology of the central nervous system is disturbed after a stroke,[14,15] the neurobiological mechanisms underlying motor learning might be perturbed as well. It is also theoretically possible that acute lesion to key brain areas transiently prevents the encoding of a new skill or its expression. If MSkL is impaired during the acute phase, it is crucial to delineate the temporal course of such a depressed MSkL period to improve the efficacy of treatments or to try using new approaches.

The first aim of this study was to determine whether patients with acute stroke could achieve MSkL with the paretic UL in comparison to healthy individuals (HIs). The second aim was to compare the evolution of MSkL and motor recovery in patients. The third aim was to explore the impact of stroke on MSkL using voxel-based lesion symptom mapping (VLSM). The fourth aim was to correlate MSkL in patients with their baseline motor and cognitive impairments to uncover potential predictors of MSkL ability.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Subjects

Before experimentation, the research was approved by the CHU UCL Namur Ethics Committee in accordance with the Declaration of Helsinki. After providing written informed consent, patients with stroke and HI participated in the study. The patients were recruited from the Stroke Unit of CHU UCL Namur. The inclusion criteria were having (1) an acute stroke on brain imaging and (2) a motor deficit of the contralesional UL. The exclusion criteria were (1) contraindication to magnetic resonance imaging (MRI), (2) previous stroke, (3) complete plegia of the UL, (4) inability to follow instructions (severe aphasia or cognitive impairment; bedside neurology evaluation), or (5) medical instability. From 555 consecutively screened patients (including transient ischemic attacks), we analyzed the data from 20 patients (see patient's characteristics, TREND checklist, and patient's flowchart in the Supplemental Material). They received acute care in the Stroke Unit and early rehabilitation consisting of ≈30 minute/day of physical rehabilitation (gait-balance training, mobilization of upper and lower limbs). Thirty-five HIs (Supplemental Material) followed the same protocol, except for MRI. None of the subjects experienced adverse effect.

Study Design

This is a nonrandomized clinical intervention study with a comparison group made up of healthy controls. The patients were included between the first and seventh days poststroke (2.4±1 days) and completed the experimental protocol over 3 consecutive days (Figure S3). In addition to an MRI evaluation, they underwent a baseline assessment (Supplemental Material) consisting of the Fugl-Meyer Upper Extremity (FMUE) Assessment,[16] apraxia screen of TULIA,[17] Montreal Cognitive Assessment (MoCA),[18] and Corsi block-tapping test forward and backward to, respectively, evaluate short-term spatial memory and spatial working memory.[19]

On the first experimental day (D1), the patients/HIs trained their paretic/nondominant UL on a MSkL task with an SAT (CIRCUIT)[20,21] that was implemented on a REAplan neurorehabilitation robot[22,23] (Axinesis, Wavre, Belgium; used for motor

measures: throughout the study, it did not deliver assistance). To quantify motor control within the same environment, they performed a REACHING task on each day. They were also repeatedly evaluated with the Box and Block test[24] and a grip force measure. Motor impairment evaluation (REACHING, BTT, and grip force) and CIRCUIT training were identically replicated on day 2 and day 3 (D3). At the end of D3, generalization was evaluated with a new version of CIRCUIT.

MSkL Task (CIRCUIT)

Over 3 consecutive days, subjects were trained with the CIRCUIT task (Figure 1, previously used with a nonrobotic setup in HI and chronic stroke patients[21,25,26] and in a pilot study in acute stroke[27]). Subjects were seated in front of the REAplan screen, with their height adjusted so that their forearm was supported by a gutter and their elbow flexed 90° with the shoulder in a neutral position. Subjects controlled the cursor's displacement with their trained UL through the REAplan handle.

The subjects were instructed to navigate a cursor inside CIRCUIT for 1 minute and to move the cursor fast and accurately (keeping the cursor within the track). On D1, day 2, and D3, they trained with 10 blocks of 1-minute interleaved with breaks of 30 seconds. On D3, after the training, they performed 3 blocks of a new CIRCUIT with the same length and difficulty to assess generalization.

Motor Impairment Task

Motor control was evaluated with a REACHING task implemented on the REAplan. One of 4 targets (±45° and ±22.5°) was displayed in a randomized order, with a straight track (10 cm) from the home position to the target. The subjects were instructed to reach to the target with their cursor as fast and accurately as possible and at the end of the reach, to hold the cursor on the target's center for 2 s. Then, they returned the cursor to the home position, and the next target appeared after a short rest period. On each day, 15 REACHING trials were performed before CIRCUIT training.

Behavioral Data Processing

The REAplan data (X and Y positions, velocity, and force exerted on the handle) were recorded at 80 Hz, stored, and analyzed offline by a custom Matlab (MATLAB, Statistics Toolbox Release 2016b; MathWorks, Inc, Natick, MA) routine.

For CIRCUIT, the speed was defined by cursor velocity (cm/s), and the error was defined as the distance (cm) between the actual trajectory (cursor) and the ideal trajectory (center of the track). The raw SAT and the ratio_{SAT} were the primary outcome measures, calculated over 3-s epochs and concatenated in 1-minute blocks:

SAT = subject's speed/subject's error (in arbitrary units).

$$\text{Absolute progression} : SAT_n - SAT_{D1T1}$$

$$\text{Relative progression } (\text{Ratio}_{SAT}) : e^{(\ln(SAT_n) - \ln(SAT_{D1T1}))}$$

For REACHING, the outcome measure was the spectral arc length (SPARC), which quantifies movement's smoothness.[28–30] The SPARC was calculated from the arc length of the power spectrum of a Fourier transformation of the velocity signal[28–30] (see details in the Supplemental Material and Figure S4). The SPARC quantifies movement smoothness and is independent from the duration of the movement. In other words, 2 movements with identical shapes of velocity profiles (eg, a gaussian for point-to-point movement) but of different path lengths and durations will have identical SPARC scores. Contrary to other metrics based on acceleration or jerk, the SPARC is valid for both discrete and rhythmic movements.[28–30]

Statistical Analysis

The analysis of CIRCUIT performance was conducted on raw and log-transformed SAT values (ratio_{SAT}) to evaluate absolute

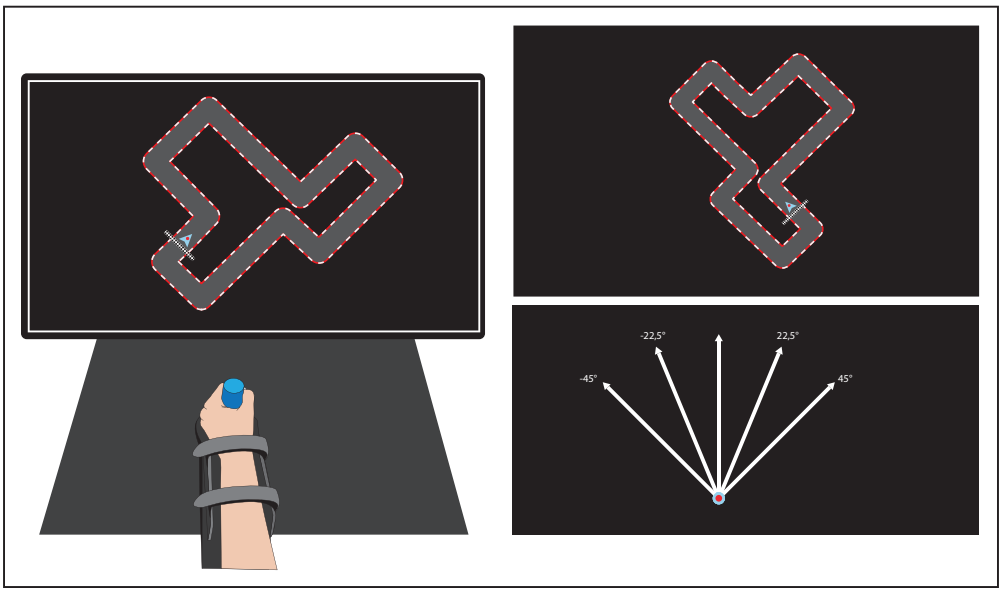

Figure 1. Task setup.
A, Neurorehabilitation robot REAplan (Axinesis, Wavre, Belgium). **B**, For the CIRCUIT task,[20,21] the subjects were instructed to navigate the cursor as fast and accurately as possible inside CIRCUIT. **C**, For the REACHING task, subjects were asked to reach as fast and accurately as possible toward each of the 4 targets presented in a pseudorandomized order.

and relative performance, respectively. Four measures were available per subject (D1T1, D3T10, G1, and G3). Generalized linear mixed models were used to compare the baselines and the progressions between patients and HI. Overall MSkL was defined as the progression between the first block of D1 (D1T1) and the last block of training on D3 (D3T10), while generalization was the progression between D1T1 and D3G1.

For patients, correlations between baseline CIRCUIT performance and impairments were computed with Pearson correlation coefficients using the MoCA score, Corsi score backward, and a Composite Motor Score (CMS). The CMS was generated using the first component of a principal component analysis performed on the FMUE, Box and Blocks test, and grip force scores of each patient to estimate the overall paretic UL impairment. Then, correlations between overall MSkL (SAT D3T10-D1T1) and the CMS and Corsi score backward were estimated.

For REACHING, changes in SPARC were estimated with another generalized linear mixed model and compared between patients and HI, both for raw SPARC and log-transformed values ($Ratio_{SPARC}$). Finally, correlations between SPARC and CIRCUIT evolutions were also estimated with Pearson correlation.

MRI and VLSM

In addition to routine clinical MRI sequences, a 3-dimensional FLAIR covering the whole brain and a diffusion-weighted imaging were acquired (details in the Supplemental Material). For each patient, a diffusion-weighted imaging volume was created, and the FLAIR image was coregistered using BrainVoyager 21.1 (Brain Innovation BV, the Netherlands). The infarcted zone (diffusion-weighted imaging positive) was manually delineated and defined as a volume of interest under the supervision of a senior neuroradiologist. The delineation used MRIcron[31] on the diffusion-weighted imaging volume in native space, thereby relying on the FLAIR volume if necessary. The FLAIR images were normalized into standard Montreal Neurological Institute stereotactic space (MNI-152), and the native volumes of interest were normalized using the same parameters. A nonparametric rank-order Brunner-Menzel analysis, using the nonparametric mapping toolbox in MRIcron, was conducted to calculate lesion-behavior relationships (VLSM). Only voxels commonly affected in at least 10% of the patients were considered. To increase the statistical power, all right sided volumes of interest were flipped to the left. The behavioral data tested for lesion-behavior relationships were the overall MSkL progression (D3T10-D1T1) in SAT and $ratio_{SAT}$ from CIRCUIT, SPARC and $ratio_{SPARC}$, REACHING, FMUE, CMS, MoCA, and Corsi block-tapping test. All the resulting maps were corrected for multiple comparison at $P<0.05$ using permutation thresholding (3000 permutations).

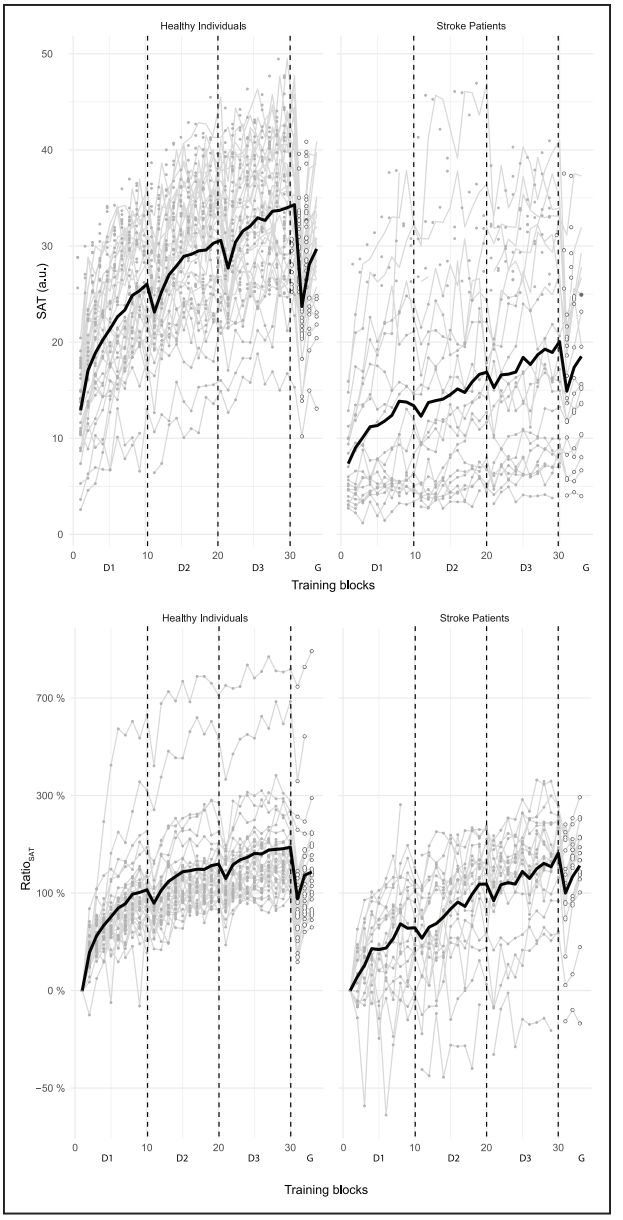

Figure 2. Motor learning in healthy individuals an acute stroke patients.
Top, Progression of the speed/accuracy trade-off (SAT; in arbitrary units [a.u.]) for the healthy individuals and acute stroke patients over 3 consecutive days (D1-D2-D3). There were slight SAT overnight drops and a larger drop between D3T10 and D3G1. Thick black line: group mean; gray lines: individuals. **Bottom**, Progression of $ratio_{SAT}$. G indicates generalization (new CIRCUIT).

RESULTS

CIRCUIT

As expected, when comparing the baseline raw SAT (in arbitrary units), the HIs performed better on D1T1 (mean±SD, 12.9±4.3) than the patients (mean±SD, 7.4±4; Figure 2A). From D1T1 to D3T10 (mean SAT progression [95% CI]), SAT improved by 21.4 (19.3–23.5) for HIs and by 12.1 (9.3–14.9) for patients. The progression between the 2 groups was statistically different ($P<0.0001$; Table S3). In contrast, the $ratio_{SAT}$ progression was not statistically different between the groups ($P=0.12$); it progressed by a factor 2.8 (2.5–3.1) in HIs and 2.5 (2.2–3.0) in patients. Some patients had large absolute and relative SAT progressions, while others showed limited/unstable progression (Figure 2B).

After completing CIRCUIT training on D3, generalization was tested with the new CIRCUIT. The raw SAT difference between the first trial of the new CIRCUIT on D3

compared with the standard CIRCUIT on D1 (D1T1 and D3G1) was 10.8 (8.7–12.9) in HIs and 6.6 (3.7–9.4) in patients. The difference between the 2 groups was statistically different ($P<0.0005$), with a bigger improvement in HIs. The $ratio_{SAT}$ improved both in HIs (1.9 [1.73–2.18]) and patients (1.9 [1.63–2.23]), without a significant difference ($P=0.81$). From G1 to G3, the SAT improved both in HIs (5.7 [3.6–7.8]) and patients (3.6 [0.7–6.5]). There were no significant differences between the groups for SAT ($P=0.07$) or $ratio_{SAT}$ ($P=0.79$).

Reaching

The HIs performed smoother REACHING movements at baseline (SPARC, 2.9±1.2) compared with patients (3.6±1.4). From D1 to D3, the SPARC improved by −1.2 (−2 to −0.4) in HIs and by −1.3 (−2.3 to −0.2) in patients (Table S3). There were no statistically significant differences between the groups for SPARC or $ratio_{SPARC}$ ($P\geq0.88$).

Correlation Analyses

Linear correlations between baseline SAT (D1T1) on CIRCUIT and impairments revealed significant positive correlations between SAT and CMS (0.72; $P=0.004$) and Corsi backward (0.57; $P=0.02$) but no correlation with the MoCA (0.17; $P=0.49$; Table S3; Figure S5). Overall progression on CIRCUIT (SAT D3T10-D1T1) correlated positively with the CMS (0.61; $P=0.005$) and Corsi backward (0.66; $P=0.002$; Figure S6). There was no significant correlation between the $ratio_{SAT}$ and the CMS or Corsi backward. Finally, there was no significant correlation (−0.32; $P=0.17$) between progression on CIRCUIT and REACHING (SPARC D1R1-D3R15).

Voxel-Based Lesion Symptom Mapping

The VLSM (Figure 3) revealed a lesion-behavior relationship for the SAT in the ipsilesional thalamus (a 452-mm^3 cluster; MNI coordinates, −17, −18, 3), covering mainly the ventral posterior lateral nucleus but extending slightly into the ventral anterior nucleus. For $ratio_{SAT}$, lesion-behavior relationships were found in the ipsilesional thalamus (a 77-mm^3 cluster covering mainly the pulvinar; −14, −24, 2) and in the posterior limb of the internal capsule (PLIC; a 31-mm^3 cluster; −19, −16, 0). These clusters were identified based on the Atlas of the Human Brain.[32] There were no significant lesion-behavior relationships for the SPARC and $ratio_{SPARC}$, FMUE, CMS, MoCA, or Corsi scores.

DISCUSSION

Motor Skill Learning

The HI showed a quick and efficient progression of the SAT, with slight overnight drops. These drops were quickly compensated, with the SAT continuously improving during each session. At the end of D3, when they experienced a new CIRCUIT, there was also a transient drop. However, the SAT on this new CIRCUIT (D3G1) was much larger than that found at D1T1, demonstrating a consistent generalization, followed by a sharply improved SAT. $Ratio_{SAT}$ followed an identical pattern. The HIs achieved typical MSkL with their nondominant UL.

The central question was to determine whether patients with acute stroke could achieve MSkL with their paretic UL during the acute period. At the group level, the results showed the same pattern as HIs on the CIRCUIT task, with steep initial improvement and slight drops overnight or when experiencing the new CIRCUIT on D3. This finding is interesting because it shows that both HIs and patients could learn and retain new motor skills, which could be of prime clinical importance. Although the patients may have benefited from early spontaneous recovery and general rehabilitation-driven improvements, these phenomena could not account for the full SAT improvements that followed the same pattern as in HIs. Therefore, overall, these results show that patients with acute stroke achieved MSkL with their paretic UL.

In absolute SAT values, the HIs had a higher baseline performance than the patients; they also achieved larger

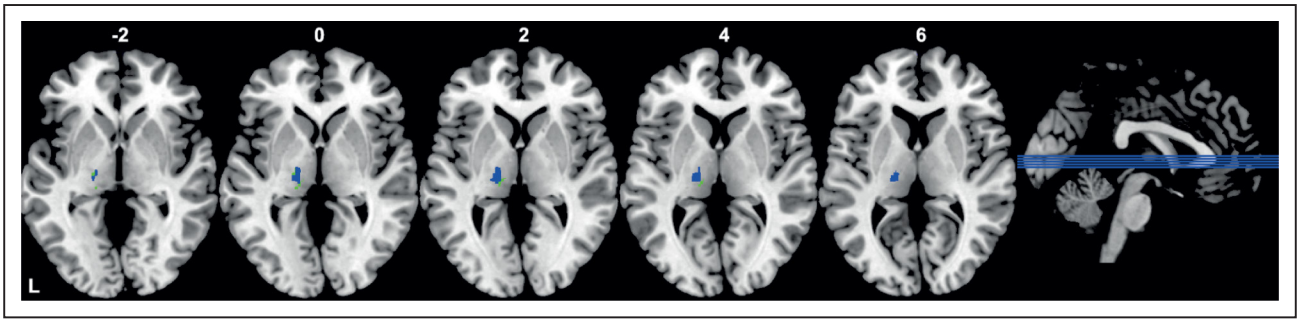

Figure 3. Voxel-based lesion symptom mapping results for the progression from D1T1 to D3T10 of the speed/accuracy trade-off (arbitrary units, in blue) and that of the $ratio_{SAT}$ (in green) projected on the Montreal Neurological Institute template ch2better.nii implemented in MRIcron.

During the acute stroke phase, more damage to the thalamus and the posterior limb of the internal capsule correlated with less efficient motor skill learning for the paretic upper limb.

MSkL over 3 days. In sharp contrast, the relative progression ($ratio_{SAT}$) was not significantly different between the patient and HI groups. The capacity to acquire and retain new motor skills with the paretic UL was thus possible in the patients and was comparable to that observed in HIs when taking baseline motor impairment into account.

However, some of the patients showed a limited/inconsistent SAT progression. The composite index reflecting global motor impairment correlated positively with both the baseline SAT and the MSkL progression (less impaired patients performed better). This is in line with the impact of sensorimotor impairments on motor performance after stroke.[33–35] A certain level of motor (control) recovery might be needed before MSkL can unfold. Interestingly, the Corsi backward score correlated positively with baseline SAT and MSkL progression, suggesting that spatial working memory is involved in the acquisition of a new MSkL with the paretic UL. The importance of spatial working memory in motor learning has been demonstrated in the early stages of visuomotor adaptation and in motor sequence learning.[36,37] Cognitive processes are increasingly recognized to play a key role in poststroke motor recovery.[38,39] Therefore, developing serious games with cognitive components might provide be interesting for neurorehabilitation involving virtual reality or robotics.[40]

Motor Control Recovery and MSkL

The REACHING task was used to evaluate baseline motor control impairment and subsequent motor recovery. Baseline movements were smoother in HIs than patients, reflecting impaired motor control for patients. However, when comparing the progression of movement smoothness between D1 and D3, HIs and patients showed a similar amount of improvement. A first explanation is that since both HIs and patients achieved MSkL on CIRCUIT, their improvements on REACHING reflect another form of generalization (a transfer). Another explanation is that the enhancement on REACHING in patients might depend on other mechanisms, such as spontaneous recovery or rehabilitation-driven recovery. However, this cannot explain the improvement in HIs. Alternatively, since both the HIs and patients were not overtrained on REACHING on D1, much room may have been left for improvement, through habituation and MSkL on the REACHING task. Whatever the underlying mechanisms, this improvement of movement smoothness of the paretic UL is encouraging for neurorehabilitation.

Voxel-Based Lesion Symptom Mapping

During the acute phase of stroke, the spared neural networks of the damaged brain may have not had time to be efficiently recruited or reconfigured. Compared with the chronic stage, there may also be less variability in the lesion-deficit associations quantified by VLSM early after stroke.[41–44] Here, the VLSM results showed that an acute stroke involving the thalamus or the PLIC correlated with less efficient MSkL with the paretic UL. The involvement of the thalamus in MSkL is consistent with a previous study using the CIRCUIT task during functional MRI in HIs, where activation in the bilateral thalamus correlated with early MSkL.[20] Similarly, stronger resting-sate functional MRI functional connectivity between the association nuclei of the thalamus and cortical motor areas correlated with better motor sequence learning in HIs.[45] The thalamus is heavily interconnected with cortical motor areas and the cerebellum and is a key node in the partly overlapping basal ganglia–cortical loops involved in motor and cognitive processes.[46–48] Acute damage to the thalamus may reduce MSkL through the integrative role of the thalamus in motor control and learning. Similarly, the finding that an acute stroke to the PLIC correlates with less efficient MSkL is consistent with the role of the corticospinal tract in both motor control and motor learning.[49,50] Interestingly, there was no significant lesion-behavior relationship for the SPARC, FMUE, and CMS, suggesting that the quantification of MSkL may reveal more subtle impairments or that a larger cohort might be needed.

Implication and Study Limitations

Many rehabilitation approaches are currently explored, including modifying brain activity through drugs or noninvasive brain stimulation,[51,52] bimanual training,[53] virtual reality, and robotics.[54,55] Robotics might be particularly interesting as they provide precise measures of subtle kinematic and dynamic changes[54,55]; deliver high-intensity training, which is deemed as a neurorehabilitation cornerstone[56–58]; and modulate task difficulty or manipulate reward and feedback based on individual progresses.[59] Our study suggests that robotics implementing the principles of motor learning could be interesting in patients with acute stroke. However, most current rehabilitation robots require the patient to be able to sit upright to interact with the robot. It would be interesting to see developments of rehabilitation robots that could be used with patients bound to the bed, especially in the early acute stroke phase.

Our patient sample size was relatively small but fair given the recruitment criterion and the difficulty to include patients with acute stroke. The inclusion period (between poststroke days 1 and 7) was relatively narrow and does not allow inference about later stages. Further studies should recruit more patients, with a broader range of neurological impairments (eg, somatosensory, cognitive), and over a longer time frame to determine whether the MSkL rate changes in days or weeks after stroke. A larger sample size would also allow more powerful VLSM analysis, which may have revealed other lesioned neural areas that predicted reduced MSkL, albeit to a lesser extent to that of the thalamus or (PLIC). Finally, patients with acute stroke may be unstable, and fluctuations in

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their performances may also reflect poor quality of sleep, cardiovascular instability, or other complications.

Conclusions

Patients in the acute phase of stroke achieved MSkL with their paretic UL and retained the improvements from day to day. Implementing the principles of MSkL into neurorehabilitation approaches, irrespective of robotic use, is feasible during the acute stroke phase. Poorer MSkL progression correlated with motor and cognitive impairments and with acute stroke involving the thalamus or PLIC.

ARTICLE INFORMATION

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Affiliations

Department of Neurology, Stroke Unit, CHU UCL Namur, UCLouvain, Yvoir, Belgium (A.R., E.G., M.G., C.D.L., Y.V.). NEUR Division, Institute of NeuroScience, UCLouvain, Brussels, Belgium (A.R., L.D., M.G.E., Y.V.). Louvain Bionics (A.R., B.H., M.G.E., Y.V.), Institute of Mechanics, Materials and Civil Engineering (B.H.), and Psychological Sciences Research Institute (M.G.E.), UCLouvain, Louvain-la-Neuve, Belgium. Scientific Support Unit (B.B., M.R.), Department of Physical Medicine and Rehabilitation (M.L.), and Department of Radiology (B.D.C.), CHU UCL Namur, UCLouvain, Yvoir, Belgium. Faculty of Medicine, Laboratory of Anatomy, Université de Namur, Belgium (Y.V.).

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Disclosures

None.

Supplemental Material

Supplemental Materials & Methods
Figures S1–S6
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