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Reduced striatal activation in response to rewarding motor performance feedback after stroke

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ABSTRACT

Introduction: Motor skill learning can help stroke survivors to cope with motor function deficits but requires many repetitions. One factor that keeps patients motivated is obtaining reward upon successfully completing a motor task. It has been suggested that stroke survivors have deficits in reward processing which may negatively impact skill learning.
Objective: To test the hypothesis that stroke survivors have deficient reward processing during motor skill learning evident in reduced activation in the striatum and its subdivisions in functional magnetic resonance imaging as compared with healthy, age-matched control subjects.
Methods: Striatal activity in response to performance dependent feedback and monetary reward was measured in 28 subacute stroke patients and 18 age-matched healthy control subjects during the training of visuomotor tracking an arc-shaped trajectory using the wrist (unimpaired side in patients, dominant side in controls) in an fMRI scanner.
Results: Despite comparable monetary rewards, stroke patients showed reduced activation in the ventral part ($p < 0.01$), but not in the dorsal part of the striatum ($p = 0.11$). 14 patients had their lesion extending into the striatum. The nucleus accumbens as part of the ventral striatum was unlesioned in all participants and still showed a marked hypoactivation in stroke patients as compared with controls ($p < 0.001$), a finding that could not be explained by motivational differences between the groups.
Conclusion: Striatal hypoactivation in stroke survivors may cause impaired consolidation of motor skills. Stronger rewarding stimuli or drug-mediated enhancement may be needed to normalize reward processing after stroke with positive effects on recovery.

1. Introduction

Stroke is a leading cause of serious long-term disability in adults by affecting motor function, speech and cognition (Benjamin et al., 2019; Chen et al., 2013). Neurorehabilitative training can be beneficial to improve independency in daily life (Veerbeek et al., 2014). This training, however, requires patient participation. Patients need to be motivated to comply with therapy (Feigenson et al., 1977). One factor that determines motivation is what patients receive in return for the training effort – the training reward (e.g., a gain in function or feedback from the environment). Often, these gains are small, occur incrementally over long periods of time and are compared against sometimes unrealistic expectations (Wottrich et al., 2012). To further augment the problem, stroke survivors may have degeneration of dopaminergic midbrain structures (Baron et al., 2014) and deficits in reward processing (Lam et al., 2016).

In healthy subjects, obtaining a reward is associated with increased striatal activation (Knutson et al., 2001, 2000; McClure et al., 2004). More specifically, intrinsic reward (e.g., performance feedback) leads to increased activation of the ventral striatum, which further increases if feedback is linked to an extrinsic reward (e.g., money) (Lutz et al., 2012; Widmer et al., 2016). Notably, in a rewarded task the neural

Abbreviations: BDI, beck depression inventory; CHF, swiss francs; DA, dopamine; EHI, Edinburgh handedness inventory; fMRI, functional magnetic resonance imaging; GLM, general linear model; IMI, intrinsic motivation inventory; MNI, Montreal neurological institute; MoCA, Montreal cognitive assessment; MRI, magnetic resonance imaging; PD, Parkinson's disease; ROI, region of interest; SD, standard deviation; SE, standard error; SSRI, selective serotonin reuptake inhibitors

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activity in the striatum correlates with striatal dopamine (DA) release (Schott et al., 2008). Animal experiments have highlighted the importance of DA for motor skill learning. Blocking DA-receptors as well as eliminating dopaminergic terminals in the rat primary motor cortex impairs motor skill learning, but not execution (Molina-Luna et al., 2009). In line with this, it has been shown that the destruction of dopaminergic neurons originating in the substantia nigra / ventral tegmental area does not affect the execution of already learned motor skills but impairs the acquisition of new ones (Hosp et al., 2011). In the primary motor cortex, dopamine facilitates long term potentiation, a form of synaptic plasticity that likely supports motor skill learning (Rioult-Pedotti et al., 2000). This hypothesis is supported by studies in healthy humans, which demonstrate that training under a rewarded condition leads to increased striatal activity (Widmer et al., 2016) and positively influences motor skill learning when compared with a control condition (Abe et al., 2011; Widmer et al., 2016).

After stroke, adding extrinsic feedback to rehabilitative training improved its effectiveness in patients that suffered from motor deficits (Subramanian et al., 2010; van Vliet and Wulf, 2006). Lam et al. (2016) demonstrated that stroke-related deficits in reward processing are reflected in impaired reinforcement learning. Whether the processing of reward derived from the performance in a motor task is also impaired after stroke, is yet unclear.

Here, using functional magnetic resonance imaging (fMRI), we investigated the neural response to performance dependent monetary reward feedback during the practice of a repetitive arc-tracking task in stroke survivors and healthy age-matched control subjects. To our best knowledge, this is the first study to test the hypothesis of a stroke-induced reduction of the striatal response (measured in pre-defined regions of interest (ROI)) to a performance-dependent extrinsic reward during a motor task.

2. Methods

2.1. Participants

Thirty-four subacute stroke survivors (50.18 ± 22.78 days post-stroke, *mean* ± *SD*) and 20 elderly (over 55 years of age) healthy adults participated in this study which was approved by the local ethics committee (EKNZ BASEC 2016–00,079). Data of elderly controls have already been compared to young adults in a previous publication (Widmer et al., 2017c) and preliminary data from stroke patients have been presented at a conference (Widmer et al., 2017b). All subjects gave written informed consent according to the Declaration of Helsinki. Severe aphasia, dementia or depression (pre-stroke) as well as uncorrectable visual disorders, for stroke patients, and psychiatric disorders or intake of central nervous drugs (e.g., antidepressants), for controls, were the exclusion criteria. Moreover, an MRI-safety-questionnaire was used to check for any MRI contraindications. All subjects were naïve to the task, received identical instructions and underwent the same study procedure. They received a financial compensation depending on their performance in the motor task.

2.2. Procedure

The study procedure and the task have already been described elsewhere (Widmer et al., 2017c). In brief, the study required one measurement session at the cereneo, center for neurology and rehabilitation in Vitznau, Switzerland. After the informed consent procedure, subjects were asked to fill in a depression-(Beck Depression Inventory, BDI II; Beck et al. (1961)) and a handedness-questionnaire (Edinburgh Handedness Inventory, EHI; Williams (1986)). Additionally, cognitive screening was performed using the Montreal Cognitive Assessment (MoCA; Nasreddine et al. (2005)). Finally, after completion of the fMRI task, subjects were asked to fill in a motivation assessment (Intrinsic Motivation Inventory, IMI, http://selfdeterminationtheory.org/intrinsic-motivation-inventory).

2.3. Motor task

To examine the processing of motor performance related reward, both groups performed a modified Arc-Pointing Task (Shmuelof et al., 2012; Widmer et al., 2017c, 2016), which allowed participants to earn money based on their motor performance while undergoing fMRI. A spherical reflective marker was attached to the index finger of the unaffected hand, for stroke patients, or the dominant hand, for the control group. This marker was continuously tracked using an MRI-compatible motion capture system (Oqus MRI, Qualysis AB, Gothenburg, Sweden) and was synchronized with a representative cursor on the screen by a computer program written in "Presentation 16.3″ software (Neurobehavioral Systems, Inc., Albany, NY, USA). Hence, by moving the wrist subjects could steer a cursor inside a semicircular ribbon (variable width, see below) in clockwise direction and in their preferred movement speed from a defined start- to an end-box while trying not to leave the ribbon.

The assessment started with a short familiarization of 20 trials, which was used to adapt the width of the ribbon in order to make sure that all participants are able to perform the rewarded task at a similar performance level. Because monetary rewards were linked to performance, this adjustment helped in balancing the amounts of money gained between the two groups. Difficulty was adjusted by narrowing the ribbon width by 12 pixels (≈0.12º visual angle) after trials with more than 70% of the trajectory inside the channel and extending the width by 12 pixels if less than 30% of the trajectory were within the ribbon. Minimal ribbon width was 12 pixels. This familiarization period was also used to make sure that all participants understood the task and were able to read and understand an example feedback as further described below.

Thereafter, each subject performed four blocks of 25 trials with a fixed ribbon width (as evaluated during familiarization) while undergoing fMRI. Subjects were shown a feedback screen including the trajectory travelled by the cursor and a monetary reward linked to their performance after 50% of the trials, or a neutral stimulus after the other half of the trials. They were unaware, however, that they were only rewarded when the performance of the current trial was better than the median of the preceding ten trials. Performance was defined as the ratio of data points lying within the channel, which was directly linked to a monetary reward in Swiss Francs (CHF). That is, if for example 80% of the trajectory lay within the ribbon (and this was better than the median of the preceding ten trials), the subject won 80 Rappen (=0.80 CHF, ≈0.8 $). After each trial, rewarding feedback or neutral stimuli (Fig. 1) were presented on a screen (0.64 × 0.4 m; 1920 × 1200 pixels) placed behind the scanner, visible to the participant via a mirror attached to the coil above their head (distance screen - mirror ≈1.90 m).

2.4. Behavioral data analysis

Ratios of data points lying within the arc-channel were averaged over 25 consecutive trials, resulting in four blocks per subject. A repeated measures ANOVA with "block" as within-subject factor (levels: 1, 2, 3 and 4) and "group" (levels: patients and controls) as between-subject factor was then calculated in SPSS (SPSS, version 23, IBM Corp., Armonk, NY, USA) and Greenhouse–Geisser correction was applied, where the assumption of sphericity was violated. For the analysis of movement durations, assumptions for ANOVA were not met, and we therefore resorted to non-parametric statistics. Finally, an unpaired two-sample *t*-test was used for the between-group comparison of the average amount of money won per rewarded trial and questionnaires were compared using the Mann–Whitney *U* test. A two-tailed value of $p < 0.05$ was considered significant.

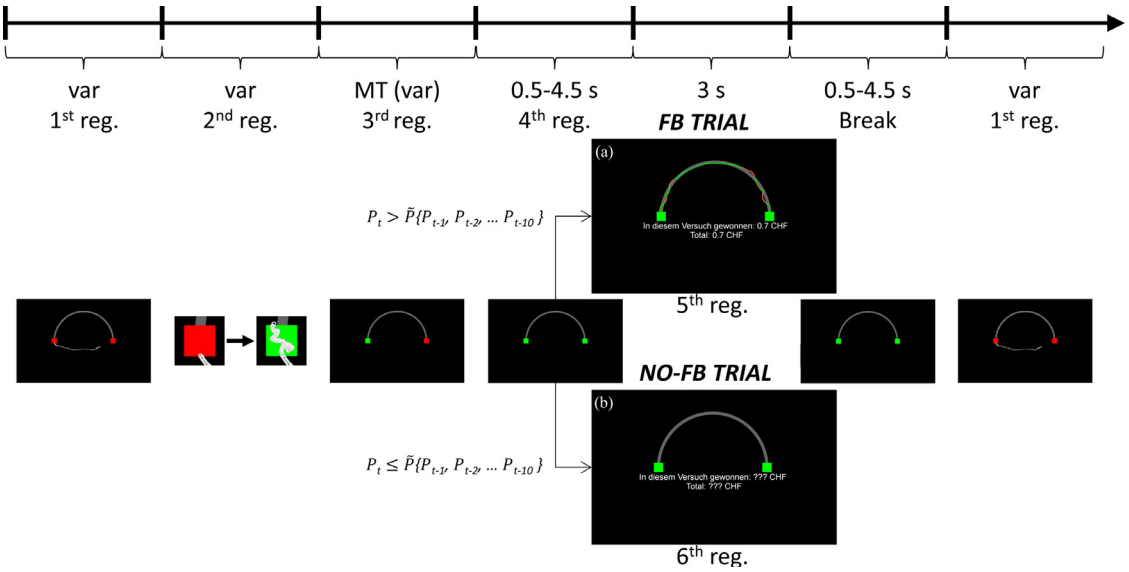

Fig. 1. Trial sequence. After placing the cursor in the start box, the box eventually turned green ("ok-to-go" signal) and subjects were free to start the movement whenever ready. The placing of the cursor in the start box, as well as the period from "ok-to-go" to the actual start of the movement were self-paced and hence of variable length (var), as was the movement time (MT) to steer the cursor through the semicircular channel. As soon as the target box was reached, the screen froze. **(a) Feedback screen** presented after feedback trials (FB TRIAL), that is, if performance of the current trial (P_t) was better than the median ($\tilde{P}$) over the previous ten trials $\{P_{t-1}, P_{t-2},\ldots,P_{t-10}\}$. The money gained in the current trial (in German: "In diesem Versuch gewonnen: 0.7 CHF") and the total money won ("Total: 0.7 CHF"), both in Swiss Francs (CHF), were presented together with the trajectory travelled by the cursor. **(b) No-feedback trial.** If P_t was not better than $\tilde{P}$, subjects were shown a neutral visual control stimulus (NO-FB TRIAL). Note that the amount of money gained in the current trial as well as the total money were replaced by three question marks and the trajectory was omitted.

2.5. fMRI data acquisition and analysis

fMRI data acquisition was performed using a Philips Ingenia 3.0T MRI scanner (Philips Healthcare, Best, The Netherlands) equipped with a 32-channel dS head coil. Before fMRI, anatomical images of the entire brain were obtained using a T1-weighted three-dimensional magnetization-prepared rapid gradient-echo (MPRAGE) sequence (170 slices, TR = 6.8 ms, TE = 3.1 ms, flip angle = 8°, FOV = 256 mm x 240 mm x 204 mm, matrix size = 256 × 240, voxel size = 1.00 mm x 1.00 mm x 1.20 mm). Subsequent fMRI data was acquired using a sensitivity encoded (SENSE, factor 1.8) single-shot echo planar imaging technique (FEEPI; TR = 2.35 s; TE = 32 ms; FOV = 240 mm x 240 mm x 140 mm; flip angle = 82°; matrix size = 80 × 80; voxel size = 3 mm x 3 mm x 3.5 mm). To establish a steady state in T1 relaxation, three dummy scans preceded data acquisition of each block. Moreover, cardiac and respiratory cycles were continuously recorded (Invivo Essential MRI Patient Monitor, Invivo Corporation, Orlando, FL, USA) to allow correction of fMRI data for physiological noise. fMRI data was analyzed using Matlab R2014a and the SPM12 software package (Statistical Parametric Mapping, Institute of Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/sp). All functional images were realigned to the first volume of the fMRI session. The anatomical image was co-registered to the mean functional image, and then segmented and normalized to the standard stereotactic space defined by the Montreal Neurological Institute. Subsequently, normalization parameters were applied to all functional images, which were resliced to 3 mm x 3 mm x 3 mm voxels, and then smoothed using an 8 mm full-width-at-half-maximum Gaussian kernel.

For first level analysis, a general linear model (GLM) was specified for each subject by defining seven recurring regressors (Fig. 1). To do so, corresponding onsets and durations were extracted from Presentation-log-files using custom Matlab routines. Moreover, correction for physiological noise was performed via RETROICOR (Glover et al., 2000; Hutton et al., 2011) using Fourier expansions of different order for the estimated phases of cardiac pulsation (3rd order), respiration (4th order) and cardio-respiratory interactions (1st order) (Harvey et al., 2008). The corresponding confound regressors were created using the Matlab physIO Toolbox (Kasper et al. (2009), open source code available as part of the TAPAS software collection: http://www.translationalneuromodeling.org/tapas/).

To compare brain activations specifically elicited by the processing of motor performance related reward, the relative signal change elicited by rewarding feedback in contrast to the visual control stimulus ("FB vs. noFB" contrast, Fig. 1), both compared to baseline activation during waiting periods, was calculated and represented as *t*-values. These were then averaged over different ROIs, using an in-house Matlab routine, resulting in an average effect size per ROI for each subject. Partitioning of the striatum in nucleus accumbens, ventral and dorsal striatum was performed according to Lutz et al. (2012), and specifically selected due to previous work, which demonstrated a main role of the ventral striatum in the reward-driven optimization of motor skill learning (Widmer et al., 2016). Briefly, ROIs from the caudate and the putamen as provided by Harvard/Oxford cortical and subcortical structural atlases were split at an axial plane through the anterior commissure (Mawlawi et al., 2001). For the caudate, the dorsal part of the head, body and tail were labeled dorsal caudate, while the part ventral of the anterior commissure was labeled ventral caudate. A similar procedure was applied to the putamen: slices dorsal to the anterior commissure were labeled dorsal putamen and slices ventral to it were labeled ventral putamen. The ventral part of the caudate and putamen together with the nucleus accumbens are functionally counted to the ventral striatum, while the dorsal part of the caudate and the putamen belong to the dorsal striatum (Knutson et al., 2008). The same definition was used here.

The resulting effect sizes per ROI were then statistically compared using SPSS. To test for significant activations, we performed one-sample *t*-tests against the null hypothesis of zero activation. A repeated measures ANOVA with "ROI" as within-subject factor (levels: nucleus accumbens, ventral striatum and dorsal striatum) and "group" (levels: stroke patients and controls) as between-subject factor was applied. Greenhouse–Geisser correction was applied, where the assumption of sphericity was violated. Significance was defined by a *p*-value smaller

than 0.05.

Either way, the next trial began after a delay period (break). Notably, onsets and durations of six of the seven regressors (reg.) are marked on the time axis (TOP). The 7th regressor was a parametric modulation of the feedback regressor by the magnitude of the monetary reward.

2.6. Lesion analysis

The boundary of the lesion was manually delineated on every consecutive axial slice showing the lesion using MRIcron software (Rorden et al., 2007) (http://www.mccauslandcenter.sc.edu/mricro/mricron/). T1 images and lesion maps were then normalized into standard MNI space utilizing unified segmentation-normalization routines of the clinical toolbox for SPM12 (Rorden et al., 2012).

3. Results

Two patients could not perform the main part of the experiment because of technical issues and another two patients had to stop prematurely, one due to claustrophobia and the other one because of fatigue. One control subject had to be excluded due to intake of drugs affecting the central nervous system. After initial analysis, two patients and one control subject were identified as outliers (*t*-value of at least one ROI < *mean* - 2**SD* or > *mean* + 2**SD*). Their data was not considered for the final analysis. Characteristics of the final sample are summarized below (Table 1).

3.1. Behavioral

Overall, learning narrowly missed significance, as revealed by a repeated measures ANOVA looking at the effect of the within-subject factor "block" (four blocks à 25 trials) on performance ($F_{2.02,\ 88.97} = 3.00$, $p = 0.05$, $\eta_p^2 = 0.06$). Both groups performed similarly (0.55 ± 0.15% vs. 0.54 ± 0.10% of data points within channel for stroke patients and healthy controls, respectively; $F_{1,\ 44} = 0.12$, $p = 0.73$, $\eta_p^2 = 0.03$) and performance developed similarly over the course of the experiment ("block*group" interaction: $F_{2.02,\ 88.97} = 0.87$, $p = 0.42$, $\eta_p^2 = 0.02$). Accordingly, patients and control subjects earned, on average, similar amounts of money per feedback-trial (0.63 ± 0.14 CHF vs. 0.63 ± 0.11 CHF; $t_{42.81} = 0.04$, $p = 0.97$, $d = 0.01$). However, the speed of the movement was self-paced and to reach a comparable performance level, stroke patients needed significantly more time as compared to controls (5.96 (5.19–8.54) s per trial vs. 4.37 (3.76–5.11) s per trial; $U = 78.0$, $p < 0.001$, $r = 0.58$).

3.2. Imaging

3.2.1. ROI analysis

For the "FB vs. noFB" contrast, both groups showed significant activations of all ROIs analyzed (Fig. 2, all $p < 0.05$). Activation was higher in control subjects ($F_{1,\ 44} = 11.45$, $p = 0.002$, $\eta_p^2 = 0.21$), although ROI-dependent ("ROI*Group" interaction: $F_{1.34,\ 58.78} = 8.32$, $p = 0.003$, $\eta_p^2 = 0.16$). Bonferroni-corrected post-hoc *t*-tests revealed that the difference was more pronounced in ventral parts of the striatum (nucleus accumbens: $t_{44} = 4.00$, $p_{corr} < 0.001$, $d = 1.18$; ventral striatum: $t_{44} = 3.27$, $p_{corr} < 0.01$, $d = 0.97$) and less clear in the dorsal striatum ($t_{44} = 2.16$, $p_{corr} = 0.11$, $d = 0.65$). To test whether fMRI activations were globally reduced in stroke subjects, the response to the neutral stimulus (noFB) was compared in the primary visual cortex (BA17) (stroke patients vs. controls: 0.68 ± 1.31 vs. 0.35 ± 1.27; $t_{44} = 0.86$, $p_{uncorr} = 0.40$, $d = 0.26$), indicating that this was not the case.

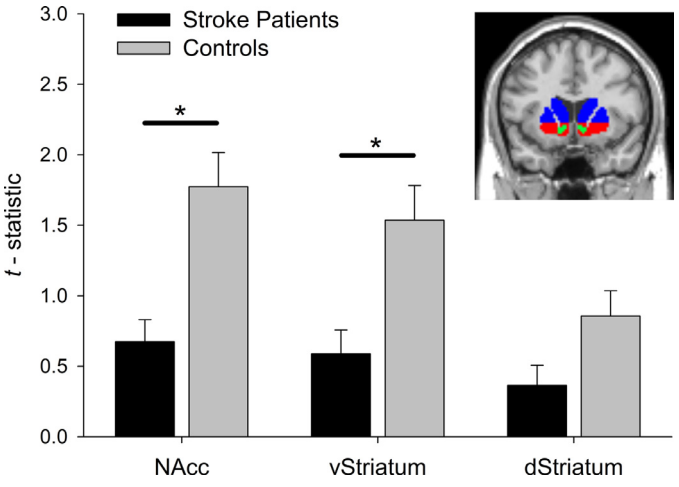

Fig. 2. t-Statistic for the "FB vs. noFB" contrast in nucleus accumbens (NAcc), ventral (vStriatum) and dorsal striatal (dStriatum) regions of interest (ROIs). $N = 28$ stroke patients and 18 controls. Mean and standard error (SE).

Results of a whole-brain analysis of the "FB vs. noFB" contrast and a table containing the ROI results broken down into "FB" and "noFB" are presented in the supplementary material.

3.2.2. Lesion analysis

The overlay of all lesions showed that the brain regions most frequently affected ($n = 7$) were the left putamen and the left caudate. Neither striatal activations nor behavioral performance were influenced by the lesion side (14 patients for each hemisphere). Lesion distribution is displayed in Fig. 3.

3.3. Motivation

Subsets of stroke patients ($n = 20$) and healthy elderly controls ($n = 9$) filled the "interest/enjoyment", "perceived competence" and "effort" subscales of the IMI, plus provided a subjective valuation of the monetary rewards linked to their performance. No differences in intrinsic motivation could be observed between the groups.

4. Discussion

Stroke patients, in comparison to healthy age-matched controls, show reduced reward-related activations in the ventral striatum when being rewarded for good performance during a motor arc-tracking task. While the ventral striatum, as a whole, was structurally damaged in 10 out of the 28 patients, the nucleus accumbens was preserved in all participants. The strong hypoactivation of nucleus accumbens can therefore only be explained by an indirect effect of the stroke on the activation pattern, not by a direct lesion to this region.

In a rewarded task, the hemodynamic ventral striatal response correlates with dopamine release in the ventral striatum, which in turn correlates with the reward-related neural activity in the substantia

Table 1
Subject characteristics, where n is the number of subjects per group, SD is standard deviation and IQR is interquartile range. Age is reported in years. Questionnaires (range, best score): BDI II, Beck Depression Inventory II (0–63, 0); MoCA, Montreal Cognitive Assessment (0–30, 30). ∗ Significant difference between groups ($p < 0.05$).

	Stroke patients ($n = 28$)	Controls ($n = 18$)
Age (mean ± SD)	60.32 ± 13.55	65.39 ± 6.40
Sex (female)	8 (28.6%)	6 (33.3%)
Handedness (right / left / bi-manual)	24 (85.7%)/2 (7.1%)/2 (7.1%)	15 (83.3%)/0 (0%)/3 (16.7%)
BDI II (median (IQR)) ∗	7.00 (4.25–9.75)	1.00 (0.00–2.25)
MoCA (median (IQR)) ∗	25.00 (22.25–26.00)	28.00 (25.75–29.00)

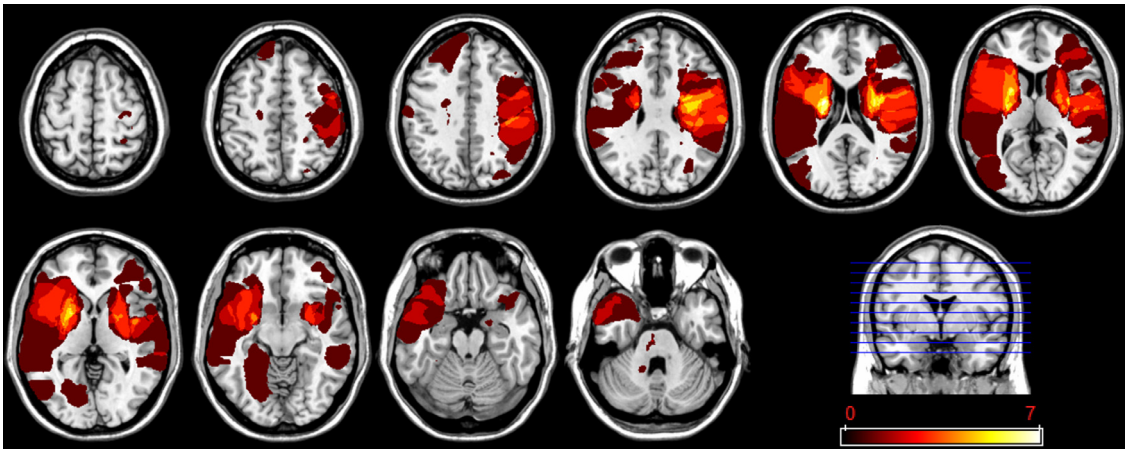

Fig. 3. Lesion distribution mapped to MNI space (z-levels: 60, 50, 40, 30, 20, 10 and 0, −10, −20, −30 from left to right for the upper and lower row, respectively) of the present patient sample (n = 28). Color bar indicates patient count.

Table 2
Results from the Intrinsic Motivation Inventory (IMI, 7-point Likert scale), presented as median (interquartile range); n is the number of subjects that filled the IMI in each group. No significant differences between groups have been found in Mann–Whitney U tests.

	Stroke patients (n = 20)	Controls (n = 9)
Interest/enjoyment	5.43 (4.00–6.07)	6.14 (5.00–6.57)
Perceived competence	4.70 (4.05–5.90)	4.40 (4.00–5.00)
Effort	6.10 (4.95–6.95)	5.40 (4.50–6.40)
IMI total	5.42 (4.58–6.02)	5.50 (4.77–5.91)
Subjective valuation of monetary reward	2.25 (1.67–2.96)	2.83 (1.83–3.42)

nigra/ventral tegmental area, the origin of the dopaminergic projection (Schott et al., 2008). The hampered reward-related activation of the ventral striatum observed here, could therefore be an indication for an impaired mesostriatal dopaminergic drive after stroke. A similar situation is observed in Parkinson's disease (PD), where it is the consequence of a degeneration of dopaminergic neurons in the substantia nigra. PD is commonly treated by administration of levodopa, a precursor of dopamine. Interestingly, unmedicated PD patients learn from punishment (Frank et al., 2004), not reward (Schott et al., 2007), whereas medicated patients learn from reward (Shohamy et al., 2005), not punishment (Frank et al., 2004). To our best knowledge, better punishment-based learning has not been shown in stroke patients (but would be well worth an investigation). Deficits in reinforcement learning, on the other hand, could be demonstrated in an earlier study using a probabilistic classification task (Lam et al., 2016). Stroke patients regardless of their age, gender or lesion location showed reduced learning, which was linked to reduced brain activation in putamen, pallidum, thalamus, frontal and prefrontal cortices and cerebellum when compared with controls.

However, based on findings from a previous trial with healthy subjects, here, we focused our imaging analysis on the striatum. In healthy young people, striatal activity has been shown to drive successful motor skill consolidation (Widmer et al., 2016). The activation of the ventral striatum can be boosted by using performance feedback in combination with monetary gains (Lutz et al., 2012; Widmer et al., 2016). Hence, such reward amplification might be applied to improve different forms of motor learning, as supported by recent work on procedural (Wachter et al., 2009) and skill motor learning (Abe et al., 2011; Widmer et al., 2016), as well as on motor adaption (Galea et al., 2015). Although their overall response to rewarding feedback, as well as their ability for reinforcement learning is reduced when compared to controls, motor recovery after stroke might still be enhanced by using such reward amplification strategies when compared with a condition where no additional feedback is given (Subramanian et al., 2010; van Vliet and Wulf, 2006). The hypothesis that rehabilitative arm training could be enhanced by rewarding feedback in the form of performance feedback and monetary gains is currently being investigated in a randomized controlled trial in the subacute stage after stroke (Widmer et al., 2017a).

According to the concepts of behaviorists, reward increases the probability that a rewarded behavior is shown in the future. Hence, rewards are closely related to motivation, providing incentives to actively seek certain stimuli (Lutz and Widmer, 2014). Motivation may rely on dopaminergic activity in the nucleus accumbens, as animal studies have shown that dopamine depletion in nucleus accumbens or low doses of dopamine antagonists reduce the willingness to work for extrinsic rewards (Salamone and Correa, 2002). However, results from the motivation questionnaire and the subjective valuation of the money gained during the experiment (Table 2) do not reflect the observed activation difference between stroke patients and controls that participated in this experiment. Moreover, nucleus accumbens activity did not correlate with IMI results for either group. As a consequence, activation differences are hardly attributable to motivational differences between the groups.

Typically, prevalence of depression is about 21%–26% in the chronic stage after stroke (Carson et al., 2000). It has been shown that the presence of post-stroke depression diminished the ability to use feedback for arm motor recovery and motor learning (Subramanian et al., 2015). In the tested sample, BDI II scores were significantly higher in stroke patients (Table 1). Still, 85.7% of the patients showed no or minimal signs of depression (score ≤ 13) and only 3 patients (10.7%) were mildly (score 14 – 28) and 1 patient (3.6%) severely depressed (> 29). The maximal BDI II score in the control sample, on the other hand, was 7. These scores, however, did not correlate with the striatal activation level in either group.

While antidepressants were an exclusion criterion for our healthy control group, many patients receive selective serotonin reuptake inhibitors (SSRI) after suffering a stroke, which has been shown to positively influence their functional recovery (Gainotti et al., 2001). In our patient sample, 17 were treated with SSRIs (mainly escitalopram). However, it has been shown that ventral striatal hyporesponsiveness during incentive cue processing in patients with major depressive disorder normalizes after successful treatment with escitalopram. Therefore, activation differences observed in the present study might have been even more pronounced if patients were not treated with antidepressants. This further supports our finding of a striatal underactivity in response to rewarding feedback reflecting motor performance after

stroke.

Cognitive deficits are a frequent consequence after suffering a stroke (Benjamin et al., 2019), as reflected by the significantly lower MoCA scores in our patient sample. These, however, did not explain a significant part of the between-subject variance and did not correlate with the striatal activation level in either group. Notably, independent from the MoCA score, it was ensured by the experimenter that each participant understands the task and is able to read and understand the feedback before each measurement.

Finally, based on our previous study with healthy subjects (Widmer et al., 2016), we would hypothesize that the reduced response of the ventral striatum observed here impairs the consolidation and hence the learning process of the trained task. Unfortunately, the design of the experiment with the somewhat vague definition of motor performance by the ratio of points lying inside the arc-channel does not allow to properly test this hypothesis, as the individual performance is influenced by the different channel sizes and the self-selection of movement speeds by the subjects. Moreover, for practical reasons the whole experiment was performed within one single session, hence not allowing to quantify overnight consolidation. Nonetheless, the manipulation of the channel size successfully equalized the performance and hence monetary gains across the two study groups, a prerequisite to validly compare striatal activations.

5. Conclusions

To conclude, subacute stroke patients as compared to healthy age-matched peers showed reduced reward-induced activation of the ventral striatum when being rewarded for good performance during a motor task. This finding could not be explained by motivational differences between the groups and was observed despite a considerable number of our patient sample was treated with SSRIs, which are assumed to compensate for reward processing deficits. This is a major finding, since the stroke rehabilitation field has been eagerly trying to use feedback and rewards to motivate patients for rehabilitative training without considering that the reward system might be altered after stroke. However, whether the reward processing deficit impairs the consolidation of the trained task and whether this potential learning deficit could be compensated by dopaminergic treatment needs further investigation.

CRediT authorship contribution statement

Mario Widmer: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing - original draft. **Kai Lutz:** Conceptualization, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation. **Andreas R. Luft:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing - original draft.

Declaration of Competing Interest

The authors report no conflicts of interest in this work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nicl.2019.102036.

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