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

Widmer, Mario; Lutz, Kai; Luft, Andreas R

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.

DOI: https://doi.org/10.1016/j.nicl.2019.102036
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Mario Widmer⁎, Kai Lutz, Andreas R. Luft

ARTICLE INFO

Keywords:
Stroke
Reward processing
Motor tracking
Performance feedback
fMRI
Striatum
Motivation

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

⁎ Corresponding author at: CARING, Cereneo Advanced Rehabilitation Institute, Vitznau, Switzerland.

E-mail address: mario.widmer@cereneo.foundation (M. Widmer).

https://doi.org/10.1016/j.nicl.2019.102036
Received 21 June 2019; Received in revised form 17 September 2019; Accepted 27 September 2019
Available online 23 October 2019
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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 naive 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 (Shmuuel 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 (≈ 0.12° 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.
trials {Pt-1, Pt-2, ...} 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 of Neurology, London, UK; http://www.nature.com/journal/v558/n7707/full/nature07317.html. The SPM12 software package (Statistical Parametric Mapping, Institute Corporation, Orlando, FL, USA) to allow correction of fMRI data for physiological noise. fMRI data was analyzed using Matlab R2014a and 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 elicted 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.
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/mricron/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 because of technical issues and another two patients had to stop pre-

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 ($F_{2,02, \ 88.97} = 3.00, \ p = 0.05, \ \eta^2_p = 0.06$). 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; $F_{1, \ 44} = 0.12, \ p = 0.73, \ \eta^2_p = 0.03$) and performance developed similarly over the course of the experiment (“block” interaction: $F_{1, \ 44, \ 88.97} = 0.87, \ p = 0.42, \ \eta^2_p = 0.02$). 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; $t_{12.81} = 0.04, \ p = 0.97, \ d = 0.01$). 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; $t = 78.0, \ p < 0.001, \ r = 0.58$).

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 ($F_{1, \ 44} = 11.45, \ p = 0.002, \ \eta^2_p = 0.21$), although ROI-dependent (“ROI” Group interaction: $F_{1, \ 34, \ 58.78} = 8.32, \ p = 0.003, \ \eta^2_p = 0.16$). Bonferroni-corrected post-hoc $t$-tests revealed that the difference was more pronounced in ventral parts of the striatum (nucleus accumbens: $t_{44} = 4.00, \ p_{cor} < 0.001, \ d = 1.18$; ventral striatum: $t_{44} = 3.27, \ p_{cor} < 0.01, \ d = 0.97$) and less clear in the dorsal striatum ($t_{44} = 2.16, \ p_{cor} = 0.11, \ d = 0.65$). 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; $t_{44} = 0.86, \ p_{cor} = 0.40, \ d = 0.26$), indicating that this was not the case.

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 nigra, striatum, and prefrontal cortex. Therefore, the dysfunction of the reward system in stroke patients may be related to structural damage in the left caudate, which was intact in all patients. The reduced activation in the left caudate, however, is not necessarily causally related to the reduced reward-related BOLD signal in the ventral striatum. It is possible that the ventral striatum was not more hypoactive because of a compensatory increase in activity in other regions, such as the prefrontal cortex, which has been shown to be involved in reward processing in healthy individuals (Ouwerkerk et al., 2014). Further research is needed to determine the exact mechanism underlying the reduced reward-related BOLD signal in the ventral striatum in stroke patients.
would be well worth an investigation). De
punishment-based learning has not been shown in stroke patients (but when compared with controls. Pallidum, thalamus, frontal and prefrontal cortices and cerebellum learning, which was linked to reduced brain activation in putamen, not punishment (Frank et al., 2004). To our best knowledge, better medicated patients learn from reward (Shohamy et al., 2005), whereas medicated 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 beboosted 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 depressed (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 IMI results for either group. As a consequence, activation differences are hardly attributable to motivational differences between the groups.

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) |

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.
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.

Supplementary materials

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

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Declaration of Competing Interest

The authors report no conflicts of interest in this work.

Acknowledgments

The authors are indebted to the volunteers for their dedicated participation in this study, which was supported by the Clinical Research Priority Program (CRPP) Neuro-Rehab of the University of Zurich and the P&K Pühringer Foundation. Furthermore, we would like to thank Samara Stulz for her contribution to the data acquisition during the performance of her Master thesis.

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.

Supplementary materials

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