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IMPAIRED IMPLICIT LEARNING AND FEEDBACK PROCESSING AFTER STROKE

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Abstract—The ability to learn is assumed to support successful recovery and rehabilitation therapy after stroke. Hence, learning impairments may reduce the recovery potential. Here, the hypothesis is tested that stroke survivors have deficits in feedback-driven implicit learning. Stroke survivors ($n = 30$) and healthy age-matched control subjects ($n = 21$) learned a probabilistic classification task with brain activation measured using functional magnetic resonance imaging in a subset of these individuals (17 stroke and 10 controls). Stroke subjects learned slower than controls to classify cues. After being rewarded with a smiley face, they were less likely to give the same response when the cue was repeated. Stroke subjects showed reduced brain activation in putamen, pallidum, thalamus, frontal and prefrontal cortices and cerebellum when compared with controls. Lesion analysis identified those stroke survivors as learning-impaired who had lesions in frontal areas, putamen, thalamus, caudate and insula. Lesion laterality had no effect on learning efficacy or brain activation. These findings suggest that stroke survivors have deficits in reinforcement learning that may be related to dysfunctional processing of feedback-based decision-making, reward signals and working memory.

Key words: stroke, classification learning, reinforcement learning, fMRI, reward, feedback.

INTRODUCTION

Ischemic brain injury is the major cause of disability in adults by affecting motor function, speech and cognition (Rosamond et al., 2007). For stroke patients, neurorehabilitative training is an effective intervention to increase independency in daily life activities (Bowen et al., 2002; Brady et al., 2012; Veerbeek et al., 2014). This training-induced reduction of impairments is mediated in part by plastic reorganization of cortical circuits (Nudo, 2003; Schaechter, 2004) and depends on the brain's ability to learn (Krakauer, 2006; Dominguez-Borras et al., 2013; Russell et al., 2013). Thus, many training principles for successful skill learning are also used in rehabilitation therapy (French et al., 2007; Orrell et al., 2007; Boyd et al., 2010; Ausenda and Carnovali, 2011).

The delivery of feedback is an important modulator of learning as pleasant and rewarding stimuli may reinforce and increase the effectiveness of learning (Wachter et al., 2009; Lam et al., 2013). Adding rewarding feedback to rehabilitative training improved its effectiveness in stroke patients that suffer from motor deficits (van Vliet and Wulf, 2006; Subramanian et al., 2010) and spatial neglect (Malhotra et al., 2013). Feedback is encoded in fronto-cortical–striatal circuits that are interlinked with structures involved in reward processing (e.g. hippocampus and amygdala) and modulation of attention (e.g. temporo-parietal cortical areas) (Mesulam, 1999; Russell et al., 2013). Patients with lesions in the basal ganglia demonstrate learning deficits and show reduced rehabilitation success (Boyd et al., 2009).

The objective here is to assess the integrity of feedback-based learning in stroke patients using an implicit probabilistic classification task (Knowlton et al., 1996) that was recently validated for healthy volunteers.

EXPERIMENTAL PROCEDURES

Subjects and task

Twenty-one healthy elderly subjects (control) and 30 stroke survivors were recruited via advertisements. An analysis of the data of control subjects was published previously (Lam et al., 2012). Stroke patients were included if they had suffered an ischemic stroke six or more months before enrollment. The presence of stroke was confirmed by MRI and diagnosed by an experienced

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Abbreviations: BDI, Beck's Depression Index; BOLD, blood oxygenation level; FDR, False Discovery Rate; fMRI, Functional magnetic resonance imaging; MMS, Mini Mental Status exam; OAS, opposite response after smiley; SAS, same response after smiley; SOS, Student opinion scale; VLBM, voxel-wise lesion-behavior mapping; WPT, weather prediction task.

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stroke-neurologist (CG). Exclusion criteria for all participants were visual impairments, a Mini Mental Status exam (MMS) < 27 points and Beck's Depression Index (BDI) > 11 points. In addition to the MMS and BDI, the Student opinion scale (SOS) and a quality-of-life questionnaire were collected. In all patients, structural MRI scans of the ischemic lesion were performed. Ten of the 21 control subjects and 17 of the 30 stroke survivors underwent fMRI testing. The study was approved by the Ethics Committee of the University of Tübingen, Germany. All participants provided written informed consent.

The weather prediction task (WPT) was performed as described by Knowlton and coworkers (1996). The task is a two-alternative forced-choice classification task in which participants learn probabilistic associations between 14 different combinations of four playing cards and two weather outcomes, sun and rain. Each card is associated with an outcome with a pre-specified probability (for sun: card 1 – 80%, card 2 – 54%, card 3 – 43%, card 4 – 20%, vice versa for the outcome rain). Either one, two or three cards are presented composing 14 different combinations that predict the weather with a certain probability. Table 1 shows for each combination of cards the probability and how often the combinations were presented during the 150-trial training period. Predictive probability was classified as high, medium or low. This stratification was done because some combinations were presented less frequently than others. By grouping we obtained prediction classes of approximately equal frequency.

Each trial consisted of the presentation of a card combination and the response of the subject – (“sun” or “rain”) by pressing one of two buttons followed by feedback in form of a smiley or a frowney face. For example, for card combination 10 (Table 1) 92% of the trials required a “sun” response and 8% a rain response to see only smileys. Otherwise, frowneys were shown. The paradigm was implemented using Matlab (Mathworks Inc, Natick, MA, USA) and Psychtoolbox (www.psychtoolbox.org).

The WPT was verbally explained and briefly trained before the experiment (on average 20 trials). This practice ensured that participants became used to the procedure. Neutral faces were shown as feedback during practice trials. Participants were instructed not to talk with the investigator during the entire experiment. After presentation of a card combination, the subject had to respond within 4 seconds or the trial was scored as “incorrect”. After 3 seconds, a prompt (“Please press a button”) appeared on the screen. After pressing either the “sun” or the “rain” button, feedback was shown for 2 s. After every 50 trials a one-minute break was allowed. One experiment included 150 trials.

Analysis of behavioral data

Trials in which the subject responded identical to a preceding trial where the same card combination had been rewarded with a smiley (same response after smiley, SAS) were counted. The two trials could have been subsequent or several trials apart. As a measure of reinforced memorization of a card combination, the ratio of the number of SAS and all smiley trials was calculated (= SAS/(SAS + OAS); OAS: opposite response after smiley). Vice versa, to examine if subjects remembered to change their response behavior after seeing a negative feedback (i.e. a frowney), we counted “opposite response after frowney” (OAF) and “same response after frowney” trials.

Trials were scored as “correct” when subjects chose the optimal response that is the more probable weather (sun or rain) for the card combination presented, e.g. for card combination 10 (Table 1) all trials in which the response was “sun” were counted as “correct”. This count was not identical to the number of responses that resulted in smiley feedback since feedback was probabilistic according to probabilities shown in Table 1. Behavioral data were analyzed by plotting the percentage of correct responses for every 30 trials to obtain a learning curve.

Additionally, reaction times between presentation of the card combination and the subject's response were recorded and compared between groups. Trials in which subjects did not respond were scored as “incorrect”. The percentage of missed responses was calculated and compared between groups.

For statistical testing Prism version 5.0 (GraphPad Inc., San Diego, CA, USA) and JMP (version 10, SAS Institute Inc., Cary, NC, USA) were used. Learning curves were compared between groups using repeated measures ANOVA. Sphericity was assessed using Mauchly‘s test and Greenhouse-Geisser (G-G) correction was applied if the test was significant. SAS/(SAS + OAS) ratios were compared using ANOVA with group as between-subject factor and pattern as within-subject factor including the interaction of the two.

Functional magnetic resonance imaging (fMRI)

A 3 Tesla scanner (Trio-Tim with 8-channel phased-array head coil, Siemens, Erlangen, Germany) was used. Visual cues were presented via a projection system installed in the scanner room. Responses were collected using an MRI-compatible button-box.

The WPT was performed in participants naïve to this task as described above except that the intertrial interval was 5 s, subjects had to respond within 4 s and did not receive written prompts. A control task was included before the WPT to record brain activity related to visual processing and movement comparable to the WPT. In the control task, one, two or three cards were shown. Subjects were asked to respond with the right button when two cards were presented and the left button when one or three cards were shown. Thirty practice trials were performed outside the scanner in which neutral faces were shown as feedback to avoid learning before the definitive experiment began. Brain activity during WPT was measured during three blocks of 50 trials each separated by 30 s of fixation. Fifty trials of the control task were performed before the WPT.

A high-resolution T1-weighted scan was acquired for anatomical localization. Functional imaging was performed using a gradient-echo planar T2*-weighted