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The effect of surgery and intracerebral injections on motor skill learning in rats - results from a database analysis

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1. Abstract

Male Long-Evans rats are often used to investigate neural mechanisms of learning in the motor system. Successful acquisition of a skilled motor task is influenced by various variables such as animal supplier and batch membership. In this retrospective analysis of our laboratory database, we investigate how head and brain surgery as well as intracerebral injections that were performed to address particular scientific questions affect motor learning. Overall, invasive interventions (n=90) slow the acquisition of a skilled-reaching task when compared to naïve animals (n=184; P=0.01). With respect to subgroups, this detrimental effect widely differs between particular procedures: whereas epidural implantations of thin-film electrode arrays and punctual injection through pre-implanted cannulas into primary motor cortex (M1) do not interfere with learning, skill acquisition is slowed after chronic infusion using osmotic minipumps into M1 and skill acquisition is lastingly impaired after bilateral cannula implantation within the dorsal striatum. In line with previous reports, breeder-specific differences could be observed in the analysis of the overall population. In summary, interventions may impair learning-behavior in an unpredictable fashion. Thus, a comparison of behavioral data to a naïve population is recommended to be aware of these drawbacks.

2. Introduction

The forelimb skilled-reaching task (SRT) is frequently used to study motor learning and plasticity in the motor system. During SRT, animals are trained to reach with their preferred forepaw towards a food pellet, to grasp and retrieve it [1]. Using this paradigm, learning-induced changes have been described with respect to gene expression [2, 3], dendritic morphology [4, 5] and synaptic plasticity [6, 7].

Successful acquisition of the SRT in rats is influenced by many factors such as animal supplier and batch effects [8]. Depending on the experimental protocol, head and brain surgery (e.g. implantation of electrodes or cannulas for administration of drugs) is required before or during training. Surgery may affect the course of motor learning by either damaging neuronal structures [9] or by causing stress [10]. These effects have to be accounted for when interpreting the data.

To measure potentially confounding effects of surgery, we retrospectively analyzed learning curves for different experiments. Interventions included epidural implantation of electrodes arrays, implantation of cannulas into the primary motor cortex (M1) or dorsal striatum (DS) and one-time injection or continuous infusion of saline into M1 or DS.

3. Materials and Methods

3.1. Animals and experiments

Data were retrospectively analyzed from 274 male Long–Evans rats that were used in several previous or ongoing experimental protocols between 2006 and 2014. These experiments investigated neuroplasticity in response to motor learning and after ischemic stroke and the data were published previously and separately ([11-18]. Rats were raised within our own breeding colony at the University of Tubingen (BC, n = 201) or were obtained from Centre d'Elevage R. Janvier, Le Genest - St. Isle, France (CEJ, n = 62) and Charles Rivers Laboratories, Inc., Germany (CR, n = 11). Animals were housed in cages in groups of three individuals in a 12/12-hour light/dark cycle (light on: 8 pm, off: 8 am). Training sessions were performed at the beginning of the dark phase. Animals were food-deprived for 24 hours prior to the first pre-training session. Daily food supplements (ca. 50 g/kg of standard diet) were given after the reach training session to maintain constant body weight. Access to water was ad libitum. All experiments were conducted in accordance with German and Swiss regulations and were approved by the local Animal Welfare and Ethics committee of the state of Baden-Württemberg and the Committee for Animal Experimentation of the Canton of Zürich.

3.2. The skilled-reaching task (SRT)

The skilled-reaching task was performed as previously described [19]. The training cage was a 15 x 40 cm acrylic glass chamber (height 30 cm) with a vertical window (1 cm wide, 5 cm high, lower edge 2 cm above ground) in the front wall and a small light sensor in the rear wall (7 cm above ground). As the motor task was embedded

in an operant conditioning paradigm, animals required a pre-training to operate the experimental setup properly. During this pre-training, animals learned to open the motorized sliding door that covered the front window by nose-poking a sensor in the rear. Opening the window gave access to one food pellet (45 mg, Bio-serve, Frenchtown, NJ, USA) located on a small horizontal board in a distance of 0.5 cm relative to the outside edge of the window. During pre-training, pellets were retrieved by tongue. Upon retrieval, a pellet dispenser automatically replaced the pellet. Pre-training ended when rats were able to initiate 100 door-openings in ≤ 30 minutes. After pre-training, forelimb preference was determined by placing the food pellet in a distance of 10 mm in front of the window. In this position pellets were only retrievable by using the forelimb. Animals were allowed to perform 20 reaching attempts - the paw that was used more frequently than the other one was defined as the preferred side. One day after forelimb preference was determined, motor training was initiated by removing the board and placing the pellet on a small vertical post 1.5 cm away from the window. The pedestal was shifted to one side of the window to allow for reaching with the preferred limb only. Because the diameter of the post was approximately that of the pellet, the pellet was in an unstable position easily kicked off the post. To retrieve the pellet rats had to extend the forelimb towards the target, pronate, open the paw, grasp, and pull the forelimb back while supinating to bring the pellet towards the mouth [1]. Each reaching trial was scored as “successful” (reach, grasp and retrieve) or “unsuccessful” (pellet pushed off pedestal or dropped during retraction). Each session consisted of 100 door openings (= trials). The improvement of reaching performance between sessions was defined as the success rate, i.e. number of successful trials/100 trials. The number of training sessions that were performed was different between experimental protocols. For the purpose of the retrospective analysis presented here seven training days were taken into account.

3.3. Description of interventions

From the 274 rats that were included in this analysis, 184 individuals were naïve with respect to treatments or interventions. However, 90 animals underwent surgical procedures before training onset or were assigned to interventions during training according to the protocol of the particular study. In case of injections, only saline was administered, as animals were assigned to the control group. After surgery, animals were allowed to recover for three days before training started. Buprenorphin was administered for pain control after all surgeries. For detailed information with respect to interventions, we refer to the particular original publications. In brief, four interventional conditions can be distinguished:

3.3.1. Electrode array implantation and cortical micro-stimulation, **Array** [12, 13]: after pre-training and the assessment of laterality, a polyimide-based electrode array was implanted epidurally over the primary motor cortex (M1) contralateral to the preferred paw (n = 18) using an osteoplastic hemicraniotomy. One day before training started, rats underwent a mapping of the motor representations using electrical micro-stimulation. During this procedure (duration: 60 to 90 minutes), rats were anesthetized using ketamine and xylazine (70/5 mg/kg, i.p.).

3.3.2. Punctual intracortical micro-injection, **M1-IN** [14]: after pre-training and the assessment of laterality, an injection-cannula was chronically implanted within the forepaw representation of M1 contralateral to the preferred limb in a depth of 900µm (n = 26). At day 2 and 3 of training, a volume of 0.5µl saline was injected over 1.5 minutes using a microsyringe and a microinjection pump.

3.3.3. Bilateral punctual micro-injections into the dorsal striatum, **DS-IN** [14, 16]: after pre-training and the assessment of laterality, injection-cannulas were chronically implanted bilaterally within the dorsal striatum (n = 32). At day 1 and 2 (n = 16) [16] or at day 2 and 3 (n = 16) [14] of training, a volume of 0.5µl saline was injected over

1.5 [14] to 5 [16] minutes using a microsyringe and a microinjection pump. Animals were allowed to recover for three days before training started.

3.3.4. Chronic intracortical infusion using osmotic minipumps, **CI-IN** [11]: after pre-training and the assessment of laterality, an injection-cannula was chronically implanted within the forepaw representation of M1 contralateral to the preferred limb in a depth of 800µm (n = 14). The cannula was connected to a pump reservoir that was subcutaneously implanted in the neck region. Pumps were loaded with 100µl saline that was continuously infused with a flow rate of 0.25µl/hour. Rats were allowed to recover for one day before training started.

3.4. Statistical analysis

Statistical analyses were performed using Prism version 5.0 (GraphPad Inc., San Diego, CA, USA) and SPSS Statistics 22.0 (IBM Corp., Armonk, NY, United States). Datasets were checked for normality using the Shapiro-Wilk test. Parameters were compared using unpaired t-tests or one-way ANOVAs. Learning curves were compared using 2-way repeated measures ANOVA with group (Naïve vs. Intervention; Array vs. M1-NI vs. DS-IN vs. M1-CI) as between- and session (training day 1-7) as within-subject factor. Sphericity was assessed using Mauchly‘s test and Greenhouse-Geisser (G-G) correction was applied if the test was significant. For learning curves, first session (day) was implemented as a covariate to avoid false-positive results caused by baseline differences. Furthermore, the parameters age, weight, litter, breeder, laterality-index (ratio of n = left-handed rats/n = right-handed rats) and experimenter were included as independent variables. Dummy variables were used for the parameters laterality, breeder and experimenter. Post hoc tests were performed using Bonferroni correction for multiple comparisons. Plateau-performance was defined as the mean of success rate from day 6 and 7. Correlations

were assessed using Pearson correlation coefficients. Numerical results are expressed as mean and standard error of the mean (SEM).

4. Results

The basic parameters characterizing the different groups within our database reflect a fair heterogeneity that is caused by the difference in study designs (Table 1). With respect to age, animals in the Naïve group were significantly younger when compared to the Intervention group (unpaired t-test: p=0.035). Within the Intervention group one-way ANOVA also revealed a significant difference with respect to age ($F(3,86)=14.39$; $p<0.0001$; post-hoc analysis: Array>DS-IN and M1-CI; M1-IN>M1-CI; M1-CI>Array, M1-IN, DS-IN and M1-IN; for all comparisons: $p<0.05$). For the parameter weight at training onset, animals from the Intervention group were significantly heavier when compared to Naïve ones (unpaired t-test: p=0.035). In the Intervention group, one-way ANOVA indicates a significant difference in weight between subgroups ($F(3,86)=3.65$, $p<0.02$; post-hoc analysis: Array<M1-IN and DS-IN). Also for laterality and experimenter a fair degree of heterogeneity between groups and subgroups has to be asserted. To avoid a confounding effect of these differences, the parameters age, weight, breeder, laterality, litter and experimenter were included as independent variables in the repeated measures ANOVAs that were conduced to assess the impact on interventions on motor learning.

When compared to Naïve animals, acquisition of the skilled-reaching task was slower in rats of the Intervention group (interaction effect of session × group: $F(6, 1632)=3.1$; $p=0.01$; Figure 1). Post-hoc test reveals a significant difference for training session 2 ($p<0.001$). Performance at plateau was not different between groups (unpaired t-test: $p=0.54$; success rate Naïve: 0.31 ± 0.01, Intervention: 0.31 ± 0.01). With respect to independent variables, a statistically significant effect was only present for the parameter breeder ($F(6,1632)=2.9$; $p=0.014$; Figure 2). Whereas BC und CEJ

animals from our own stock (BC) and Centre d'Elevage R. Janvier (CEJ) show similar learning curves, animals derived from Charles Rivers Laboratories (CR) show a lower motor performance on day 2 and 3 (not statistically significant in the post-hoc analysis). However, as CR rats were equally distributed among groups (Naïve: 4%; Intervention: 7%), this should not have affected the result of the overall analysis.

The type of intervention significantly influenced the acquisition of the skilled-reaching (interaction effect of session × group: $F(18, 522)=3.0$; $p<0.0001$). Performance at plateau was significantly different between groups ($F(3,86)=5.3$; $p=0.002$; post-hoc analysis DS-IN< Array ($p<0.01$) and < M1-IN ($p<0.05$); success rate Array: 0.36 ± 0.02, M1-IN: 0.35 ± 0.02, DS-IN: 0.26 ± 0.02, M1-CI: 0.33 ± 0.04). Thus, whereas the learning curve of Array and M1-IN animals is similar to that of Naïve animals, skill acquisition is slowed for the M1-CI group and impaired in DS-IN rats (Figure 3). With respect to independent variables, a statistically significant effect was only present for the parameter weight ($F(6, 522)=3.1$; $p=0.026$). To assess the influence of weight on motor learning, rats from the Intervention group were stratified into three groups (Figure 4A), ANOVA shows a non-significant trend for the factor weight ($F(2,87)=3.0$; $p=0.054$) to the disadvantage for lightweight rats (i.e. < 265g). However, if these lightweight rats were excluded from the analysis, the interaction of session x interventional group remained significant ($F(18,516)=2.43$; $p=0.001$) and the impaired acquisition of SRT in DS-IN and M1-CI persists (Figure 4B).

5. Discussion

Based on the retrospective analysis of our laboratory database, invasive interventions slow the acquisition of a skilled-reaching task when compared to naïve animals. However, this detrimental effect differs among particular procedures - whereas epidural implantations of thin-film electrode arrays and punctual injection through pre-implanted cannulas don't seem to interfere with learning, skill acquisition was markedly slowed after chronic intracortical infusion using osmotic minipumps and even impaired after bilateral cannula implantations within the dorsal striatum. For rats that received interventions, initial low weight was associated with poor learning successes. In line with previous reports [8], breeder-specific differences could be observed in the analysis of the entire population.

Despite to the complex surgical intervention including hemicraniotomy, implantation of polyimide thin-film electrode arrays did not perturb the acquisition of the skilled reaching task. This is in line with previous observations in a smaller population of animals [12] and can be explained by the lack of cortical damage after epidural implantation.

As assessed histologically, intracortical implantation of injection cannulas only cause minimal damage to cortical tissue [20]. With respect to stereotactic coordinates of implantation, the diameter of the implanted cannula and the amount of surgical trauma, no differences should exist between M1-IN and M1-CI conditions. As subcutaneous implantation of pump reservoirs per se did not affect behavior and learning the Morris water maze task in rat pups [21], this factor should also be not attributable for differences between the two groups. Thus, the only relevant difference is the way of fluid volume injection: whereas M1-IN rats were injected at

day 2 and 3 half an hour before the training session started, saline was continuously administered via osmotic minipumps in M1-CI rats. Measuring the uptake of 2-deoxyglucose revealed the presence of a zone of glucose hypometabolism that was 3 mm in diameter and exceeded the implantation scar (0.4 mm) in a similar experimental setting when compared to our study [22]. Thus, chronic infusion seems to interfere with plastic processes by reducing glucose metabolism in a widespread cortical area finally resulting in a slower acquisition of motor performance.

Interestingly, bilateral implantation of injection cannulas into the dorsal striatum and consecutive saline injections perturbed motor learning stronger than implantation/injection of M1 contralateral to the trained paw. Moreover, a lasting impairment in skill acquisition as indicated by a lower performance plateau was present in the DS-IN group. This is surprising, as M1 is thought to be the structure where motor memories become stored [23]. As histology showed only minimal injury through cannula implantation [16], the amount of surgical trauma is also not an appropriate explanation. However, M1 and dorsal striatum are heavily interconnected [24, 25] and striatal plasticity also contributes to motor learning [26, 27]. Furthermore, inhibiting protein synthesis within the dorsal striatum impaired the acquisition of the SRT [16]. Thus, these data show that even small lesions in remote - but functionally connected areas may severely impact the readout in behavioral studies.

That breeder-specific differences in skill acquisition were found in our analysis is in good agreement with previous reports [8]. There, rats that were delivered by Charles Rivers Laboratories (CR) showed the slowest learning performance. This was also observable in our retrospective analysis, even though the total number of CR animals was low (n=11). In our dataset we did not observe a significant effect of litter, whereas O'Bryant et al. reported an effect for batch. “Batch” was defined as the sum

of litters that were purchased at one time for a defined experimental purpose. In our documentation, each litter was indicated separately and littermates were usually equally distributed across experimental groups. Thus, analysis of batch and litter can be hardly compared between the two studies. Also in contrast to O'Bryant and colleagues, a non–significant tendency towards a relation between small weight and poor performance was present in the subpopulation of rats that received an intervention. In principle, reduced body weight due to dietary restriction may impair motor performance [28]. However, as age is inversely correlated with weight in our dataset (R^2 = 0.06, p=0.04), the lower weight can be likely attributed to the younger age and not to dietary factors. Younger rats are thought to show a better performance in learning and memory tests when compared to older animals [29, 30]. Furthermore, the factor age did not show any significant effect in the ANOVA and the differences between subgroups remained significant even though lightweight animals were excluded from the analysis. Thus, the impact of weight in the Intervention group cannot be finally interpreted but should not have confounded the result of our analysis.

6. Conclusion

This study shows that invasive interventions may slow and even impair skill acquisition in a rat model of motor learning. However, as this detrimental effect is only present in particular paradigms, it is hard to predict how an invasive procedure will influence the behavioral readout. For example, chronic infusion of fluids may create a widespread zone of hypometabolism and even small interventions in strategically important areas may induce lasting impairments in skill acquisition. Researchers should be aware of these methodological shortcomings e.g. by comparisons with a naïve population. If feasible with the purpose of the experiment, changing procedures (e.g. punctual vs. chronic infusion) may then reduce the confounding effect of interventions.

7. Tables

	Naïve	Intervention				
		pooled	Array	M1-IN	DS-IN	M1-CI
n	184	90	18	26	32	14
Age (d)	106.9 ± 1.8	100.6 ± 2.3	114.5 ± 4.8	106.6 ± 4.0	99.3 ± 2.8	74.4 ± 5.5
Weight (g)	287.8 ± 4.3	302.5 ± 4.5	324.3 ± 8.8	316.3 ± 9.4	299.1 ± 5.8	256.9 ± 5.1
Litters (n)	47	37	13	9	12	3
Laterality index (left/right)	0.53	0.53	0.83	0.42	0.41	0.64
Breeder	BC, CEJ, CR	BC, CEJ, CR	BC, CR	BC, CR	BC, CR	BC, CEJ, CR
Experimenter initials	AL, BH, CO, KM, MB, MS, SR	AL, AP, BH, KM, MB, MS, SH, SR, TW	AL, BH, KM, MB	BH, KM, MB, MS	KM, SR, TW	AP, SH

Table 1. Baseline characteristics and parameters of groups/subgroups from different studies extracted from our database. The laterality-index was calculated as the ratio of n = left-handed rats/n = right-handed rats. BC: own breeding colony; CEJ: Centre d'Elevage Janvier; CR: Charles Rivers Laboratory. Values represent mean ± SEM.

8. Figures legends

Figure 1. Acquisition of the skilled-reaching task was slower in the intervention group when compared to naïve rats. Whereas post-hoc analysis shows a significant difference for training session two, performance at plateau was not different between groups. *:p<0.001. Values represent mean ± SEM.

Figure 2. Reaching performance depended on the originating breeding colony. Whereas BC und CEJ animals show similar learning curves, CR animals show a lower motor performance on day 2 and 3 (not statistically significant in the post-hoc analysis). Values represent mean ± SEM.

Figure 3. The type of intervention significantly influenced the acquisition of the skilled-reaching task. Whereas the learning curve of Array and M1-IN animals is similar to that of Naïve animals, skill acquisition is slowed for the M1-CI group and impaired in DS-IN rats. Values represent mean ± SEM.

Figure 4. (A) When rats of the Intervention group were binned with respect to their initial weight, a (statistically non-significant) trend exists to the disadvantage for lightweight rats. **(B)** When lightweight rats (<266g) were excluded from the Intervention group, the slowed acquisition of SRT in M1-CI and the impaired acquisition in DS-IN rats persist. Values represent mean ± SEM.

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