Clinical outcomes following stroke are influenced by stressful experiences. Here we report that stress interacts synergistically with focal ventrolateral striatal ischemic injuries to disrupt skilled movement and spatial performance. Stress and ischemic injury were induced by restraint and endothelin-1 infusion, respectively, in adult male Long–Evans rats. The ziggurat task, a dry-land version of a skilled reaching task, was used in post-stroke assessment. Ischemic injury impaired skilled movement and spatial performance. However, stress prior to ischemic injury significantly exaggerated these deficits. Importantly, stress exacerbated ischemic injury to a degree that appeared additive, that is, stress and ischemia together produced deficits significantly greater than those seen following stress or ischemia alone. Synaptic plasticity measures indicate that the regionally selective effects of ischemia were similar whether or not stress was involved, suggesting that the severe deficit seen in the dual condition was due to a stress-related exacerbation of ischemic effects. Both dorsal and ventral striatum assist in the control of stress responses and regulate their psychophysiological consequences. Thus, damage to the striatum may disturb the central processes of stress control and enhance its adverse psychological and physiological effects. Regionally selective striatal lesions, predominantly to its dorsal portion, have been linked to behavioral deficits. It is not clear whether spatial and motor deficits are evident after lesions in the ventral striatum. Both dorsal and ventral striatum assist in the control of stress responses and regulate their psychophysiological consequences. 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deficits in skilled forelimb use. By contrast, we provide evidence that the synergy between ventrolateral striatal stroke and stress does not have a significant impact on spatial performance.

Material and methods

Subjects

Twenty-two adult male Long–Evans rats, weighing 380–420 g at the beginning of the experiment, raised at the Canadian Centre for Behavioural Neuroscience Vivarium at the University of Lethbridge, were used. The animals were housed in pairs under a 12:12 h light/dark cycle with light starting at 07:30 h and temperature set at 22 °C. All testing and training were performed during the light phase of the cycle at the same time of day. The animals received water ad libitum. Animals were food-restricted one week prior to baseline training, and maintained at about 90% of their initial body weight throughout the experiment. Rats were given an additional amount of food in their home cage at least 4 h after completion of the behavioral training and testing. Because animals were housed in pairs, they were weighed daily throughout the experiment in order to monitor their food consumption. Each rat was handled for five consecutive days prior to any experimental manipulation. All procedures were performed under protocols approved by the Animal Care Committee of the University of Lethbridge in compliance with the guidelines of the Canadian Council on Animal Care.

Experimental design

The rats were trained in skilled forelimb reaching task for 28 days in order to establish a reliable baseline for limb preference before surgery. Once their performance reached a plateau after 4 weeks of pre-stroke training, the animals’ performance was video recorded for qualitative movement analysis (Metz and Whishaw, 2000). Animals were then randomly assigned to the following groups: sham (N = 5), stroke-only (N = 6), stress-only (N = 6) and stroke + stress (N = 5). Animals assigned to the striatal stroke groups (stroke-only, stroke + stress) received an endothelin-1 (ET-1) injection into the ventrolateral striatum on the side contralateral to the paw preferred for reaching. The sham group received all surgical procedures except ET-1 infusion. The stress group only received post-stroke stress treatment.

Blood samples and restraint stress

Blood samples

All procedures for blood sampling and restraint stress were similar to those reported by Faraji et al. (2009). Blood samples were taken at baseline (the day prior to stress treatment) and 15–20 min after restraint on day 21 of daily stress. All samples were collected in the morning hours. Rats were transported individually to the surgical suite and anesthetized with 4% isoflurane. During the 2–3 min of anesthesia, 0.6 mL of blood was collected from the tail vein. Blood was sampled using a heparinized butterfly catheter. Blood samples were transferred to centrifuge tubes and plasma was obtained by centrifugation at 5000 rpm for 5 min. The plasma samples were stored at −20°C until analyzed for corticosterone (CORT) levels using commercial radioimmunoassay kits (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, USA).

Restraint stress

The stress-only and stroke + stress animals were exposed to restraint stress for 21 consecutive days. Each day, animals were placed in transparent Plexiglas tubes (6 cm inner diameter) of adjustable length, from 10:00 am to 11:00 am. The tubes maintained animals in a standing position without compression of the body while allowing ventilation through perforated ends of the tube.

Spatial performance in the ziggurat task (ZT)

In order to assess spatial performance of the animals, all rats were tested in the standard version of the ziggurat task (ZT), a dry-land task for spatial cognition (Faraji et al., 2009, 2010). The training and testing procedures of the ZT to assess spatial performance were previously described in detail (Faraji et al., 2008). Briefly, the testing sessions were conducted over 9 consecutive days. The cycle consisted of alternating different-goal or learning days (odd days or days 1, 3, 5, 7) and same-goal or memory days (even days or days 2, 4, 6, 8). On the odd
days, the goal ziggurats were located in a new location, and rats had to find and learn the location of the goal ziggurat in the new place. The goal ziggurats remained in the same place on the even days. Thus, the rats were required to remember the location they had learned previously.

Two sets of ziggurats were defined in the environment. First, “start” ziggurats, located in each corner, and second, the remaining ziggurats or “goal” ziggurats. On the testing days, the rats, released from each starting point, were allowed to explore the environment. One goal ziggurat (peripheral or central) was baited with spaghetti for each trial. During each testing day, the exploration took place in eight trials per rat and at four different starting points at a randomized position. Across trials, the starting location varied among the four corners of the apparatus, and on each trial, animals navigated in the environment for 70 s or until they found the goal ziggurat and consumed the food. Since the location of the goal ziggurat remained constant from trial to trial every two days, the rats had to learn and remember the new locations of the goal ziggurat following each two days. In order to minimize olfactory cues, both the box and ziggurats were cleaned with 5% alcohol after testing.

Probe trial-dependent behaviors in the ZT were measured on the ninth day as an additional measure for spatial memory performance. The percentage of time rats spent in trial two in each quadrant of the ziggurat task was recorded.

The movements of the animals including latency or time spent to find the goal ziggurat, path speed and percentage of time spent in each quadrant on probe trials within the ZT were recorded and analyzed by a video tracking system (HVS Image 2020, UK) and an Acer computer (Travel Mate 225X). It should be pointed out that because latency and path length consistently reveal similar profiles of spatial navigation within wet- and dry-land tasks (Vorhees et al., 2004; Kapoor et al., 2009; Harrison et al., 2009; Faraji et al., 2010), we have considered and reported only latency and path speed in the ZT.

**Histology**

All animals were sacrificed by an overdose of sodium pentobarbital (300 mg/kg IP) and perfused transcardially with 0.9% phosphate buffered saline (PBS; 200 mL) followed by 4% paraformaldehyde (PFA; 200 mL). Brains were removed, post-fixed for 24 h in 4% PFA, and stored in 30% sucrose-formalin solution for cryo-protection until they were sectioned on a cryostat microtome at a thickness of 40 μm. Every fourth section was mounted on glass slides and stained with cresyl violet. The stained sections were examined under a microscope (Zeiss, Germany) and images were captured using an AxioCam camera (Zeiss, Germany) to quantify lesion extent.

The extent of striatal damage in each stroke rat was calculated. In this experiment, five images were captured under 1× magnification, corresponding approximately to 2.20, 1.20, 0.48, −0.30 and −0.92 mm relative to bregma. A systematic sampling grid with an area per point of 20,000 pixels was randomly projected on each image and the number of points hitting intact striatal tissue was counted. Grids were generated using ImageJ software. The total number of hits in each rat was then divided by the average number of hits obtained by three control rats. The complement proportion was used as the percentage striatal lesion estimate.

**Statistical analysis**

Statistical analysis was performed using SPSS for Windows 11.5.0 (Standard Version, 1982–2002; SPSS Inc., USA). The results were subject to the analysis of variance (ANOVA) for repeated measures across test-time points (SHAM: 284±33.12 ng/mL; STROKE-only: 266±83.41 ng/mL; STROKE+STRESS: 258±43.57 ng/mL). Plasma CORT values are the mean values of the eight trials. Latency, speed and percent time spent in the target quadrant were the dependent variables. Moreover, percent success, reaching attempts, and total and detailed movement scores in skilled reaching were analyzed as dependent variables for post-stroke motor alterations. Post-hoc (Tukey HSD) test was used for both memory and motor measures to adjust for multiple comparisons. In addition to the behavioral measures, for all histological data, the differences in between-group and within-group comparisons were assessed with independent and dependent sample t-tests, with P<0.05 set as the significance level. All data are presented as mean ± standard error of the mean.

**Results**

Restraint stress does not affect the extent of ET-1-induced tissue loss in the ventrolateral striatum

The ET-1 injection resulted in tissue loss limited to the striatum in all stroke animals. Fig. 1(ABC) illustrates a representative ventrolateral striatal lesion in three rostrocaudal coronal sections at 1.60 mm, 0.20 mm, and −0.80 mm from bregma, and a coronal section of the striatum in a stroke rat (Fig. 1D). The damage to the ventrolateral striatum was pronounced in all rats. No noticeable damage was found in the claustrum and dorsal endopiriform nucleus in stroke animals. No detectable tissue damage was observed in SHAM and STRESS-only groups. An analysis performed on the percent tissue loss in the striatum using volumetrics showed no significant difference between STROKE-only and STROKE + STRESS groups (17.61% ±0.97 vs. 19.04±5.85% ±1.22; P>0.58). This suggests that post-stroke restraint stress did not have any reliable impact on the structural outcomes induced by ET-1 injection into the ventrolateral striatum.

Chronic restraint stress elevates plasma CORT

There was no significant effect of Group for plasma CORT at the pre-stress time point (SHAM: 284±33.12 ng/mL; STROKE-only: 266±83.41 ng/mL; STROKE+STRESS: 258±43.57 ng/mL).
38.16 ng/mL; STRESS-only: 291 ± 33.39 ng/mL; STROKE+STRESS: 276 ± 51.24 ng/mL; P = 0.82, ANOVA). CORT levels at the post-stress time point (SHAM: 303 ± 47.22 ng/mL; STROKE-only: 292 ± 42.66 ng/mL; STRESS-only: 397 ± 50.39 ng/mL; STROKE+STRESS: 429 ± 57.81 ng/mL), however, showed a significant between-group effect \( F(3,18) = 5.11, P < 0.041; \) ANOVA indicating that the 21-days restraint stress paradigm used in this experiment enhanced plasma CORT in both STRESS-only and STROKE+STRESS groups. No significant difference was found between the STRESS-only and STROKE+STRESS groups for plasma CORT at the post-stress point (SHAM: 303 ± 47.22 ng/mL; STROKE-only: 292 ± 42.66 ng/mL; STRESS-only: 397 ± 50.39 ng/mL; STROKE+STRESS: 429 ± 57.81 ng/mL, \( P = 0.63, \) post hoc). In addition, a comparison between pre- and post-stress points for STRESS-only and STROKE+STRESS groups indicated that the restraint stress significantly enhanced plasma CORT in both groups \( \text{STRESS-only: } t = 2.29; \text{STROKE+STRESS: } t = 1.83, \) both \( P < 0.05; \) dependent sample \( t \)-test].

**Synergy between stroke and stress does not alter spatial performance**

**Latency**

Latency or time spent to find the goal ziggurat in the standard version of the ZT (Fig. 2A) was assessed. Fig. 2(B) shows the mean latencies across eight testing trials in the ZT. In addition, panel C in Fig. 2 depicts latency for all groups over the acquisition (learning) and retrieving (memory) days. A repeated measures ANOVA was performed with group, testing days and trials as independent variables, and latency to find the goal ziggurat over 64 trials of the ZT testing as the dependent variable. Our analysis showed no significant difference between groups \( F(3,18) = 0.591, P > 0.05 \) indicating that all experimental groups could remember the previous

**Path speed**

Because latency can be potentially affected by differences in path speed and, more importantly, both stress and ischemia-induced hyperactivity have previously been reported \( \) [Strekalova et al., 2005; Plamondon et al., 2008], path speed, in addition to latency, was considered within the ZT. All four groups showed relatively constant speeds across the 8 testing days in the ZT. No significant main effect of Group in terms of path speed (SHAM: 0.128 ± 0.019 mt/s; STROKE-only: 0.133 ± 0.049 mt/s; STRESS-only: 0.129 ± 0.016 mt/s; \text{STROKE+STRESS: } 0.134 ± 0.049 mt/s; \text{ANOVA: } F(3,18) = 0.86, ANOVA) was found in the task, supporting the idea that neither of the experimental manipulations (i.e. stroke, stress, and stroke + stress) in the current study had a major impact upon the animals’ speed during spatial performance in the ZT.

**Probe trial**

The percentage of time spent in the target and opposite quadrants (quadrant 3 vs. quadrant 1) of the ZT during the probe trial (day 9th) is depicted in Fig. 2(D). Analysis of the 60 s of the probe performance in the ZT revealed that all groups spent a considerable proportion of their time searching in the target quadrant. A repeated measures ANOVA conducted for the percentage of the time spent in the target quadrant (SHAM: 37.26% ± 3.82%, STROKE-only: 48.50% ± 4.18%, STROKE+STRESS: 38.83% ± 3.82%, \text{ANOVA: } F(3,18) = 0.328, P > 0.05) showed no significant effect of Group indicating that all experimental groups could remember the previous
location of the goal ziggurat. Furthermore, animals in all groups showed significant savings for the target quadrant (quadrant 3) relative to the opposite quadrant (quadrant 1, SHAM: $t = 4.08$; STROKE-only: $t = 3.64$; STRESS-only: $t = 4.91$; STROKE + STRESS: $t = 4.22$; all $P < 0.05$, dependent samples t-test). In summary, all rats tended to preferentially navigate in the quadrant in which the goal ziggurat had been presented during the previous training days.

**Stroke and stress synergistically diminish skilled reaching performance**

**Quantitative assessment (success rates and reaching attempts)**

Rats’ motor behavior was assessed by the skilled reaching task (Fig. 3A) in which animals were required to reach and retrieve food pellets with the forelimb contralateral to the striatal lesion. No significant difference between the groups in percent success was found during pre-stroke sessions [$F(3,19) = 2.75$, $P > 0.05$; ANOVA]. As illustrated in Fig. 3(B), the improvement in success rate in the pre-stroke trials from days 1 to 28 (SHAM: 20.58 vs. 58.33; STROKE-only: 22.00 vs. 57.00; STRESS-only: 24.16 vs. 68.33; STROKE + STRESS: 29.16 vs. 54.16) indicated that all experimental groups were able to improve their reaching skills as the training was proceeded.

Reaching success rates in the post-stroke sessions, in contrast, revealed a different profile of motor behavior in the experimental groups. As can be seen in Fig. 3(B), rats in SHAM, STROKE-only and STRESS-only groups were able to show significant spontaneous improvement compared to the STROKE + STRESS group. A significant main effect of Group was observed in terms of success present in stroke trials (SHAM: 62±3.92, STROKE-only: 64±3.32, STRESS-only: 70±4.26, STROKE + STRESS: 67±4.17; $P > 0.05$). An analysis conducted for post-stroke reaching attempts, however, revealed a significant main effect of Group [$F(3,18) = 8.05$, $P > 0.05$; ANOVA]. No significant difference was observed between SHAM and STROKE-only groups (53±4.16 vs. 58±5.49; $P > 0.05$, post-hoc Tukey HSD) at the post-stroke time point. Post-hoc analysis also indicated a significant difference between these two groups and STRESS-only and STROKE + STRESS groups (all $P > 0.05$) suggesting that the latter groups performed more reaching attempts than the SHAM and STROKE-only groups. In addition, while both STRESS-only and STROKE + STRESS groups had increased reaching attempts in post-stroke trials (STRESS-only: 83±5.33,
STROKE + STRESS: 79 ± 4.21), no significant difference was observed between these groups (P>0.05, post-hoc Tukey HSD). This indicates that reaching attempts in rats with mere stress and stroke + stress were equally affected by restraint stress. Furthermore, within-group comparisons between pre- and post-stroke trials revealed that only SHAM animals performed significantly fewer reaching attempts during the post-stroke period (62 ± 3.92 vs. 53 ± 4.16; t = 9.42, P<0.05; dependent samples t-test). The STROKE-only group performed fewer reaching attempts in the post-stroke period, but dependent samples t-test for pre- and post-stroke comparison showed no significant difference between trials (64 ± 3.32 vs. 58 ± 5.49; t = 12.67, P<0.05). In contrast, both STRESS-only and STROKE + STRESS groups showed increased attempts during post-stroke trials compared to pre-stroke period (STRESS-only: 70 ± 4.26 vs. 83 ± 5.33; t = 10.72; STROKE + STRESS: 67 ± 4.17 vs. 79 ± 4.21; t = 8.40, both P<0.05; dependent samples t-test).

Qualitative assessment (total and individual movement scores)

Fig. 4(A and B) compares movement performance in the skilled reaching task prior to and after stroke. Both total and individual movement scores were considered as qualitative measures for skilled limb use. There was no significant difference between groups at the pre-stroke time point [F(3,19) = 1.97, P>0.05; ANOVA]. However, analysis for post-stroke reaching performance indicated a significant main effect of Group [F(3,18) = 3.20, P<0.05; ANOVA] in which only the STROKE + STRESS group had an overall significantly lower 35-point qualitative score when compared to STRESS-only, STROKE-only and SHAM groups (all Ps<0.05, post-hoc Tukey HSD; Fig. 4Aa). Furthermore, animals in the STROKE + STRESS group had remarkably, but not significantly, lower movement scores at the post-stroke sessions when compared to pre-stroke sessions (19.26 ± 2.43 vs. 27.44 ± 1.00).

In addition, analysis of 11 reaching components at pre- and post-stroke time points indicated a similar profile in performance after stroke and stress. As illustrated in Fig. 4A, there was no overall Group difference in the reaching components at the pre-stroke time points. The difference between groups in terms of movement components at the post-stroke time point (Fig. 4B), however, was significant [F(3,18) = 5.22, P<0.05; ANOVA]. The STROKE + STRESS group showed significantly reduced movement scores when compared to STRESS-only, STROKE-only and SHAM groups (all Ps<0.05; post-hoc Tukey HSD). This effect may have originated from the lower scores in four reaching sub-components observed only in the STROKE + STRESS animals. At the post-stroke time point, rats in the STROKE + STRESS group had significantly lower Grasp, Supination I, Supination II and Release scores when compared to other experimental groups (all Ps<0.05; post-hoc Tukey HSD). These findings indicate that rats in the STROKE + STRESS group required more integrated movements of digits and paws to withdraw the pellets through the slot as well as more extensive head and body movements to extract the pellet from the paw (Fig. 5). Compensatory adjustments included an angular body position during reaching.

Fig. 4. Qualitative analysis of reaching movements in the single pellet reaching task at (A) pre-stroke and (B) post-stroke time points. Panel A shows total movement score assessed by a detailed 35-point scale before and after stroke for all groups. Rats with stroke and stress had lower total reaching scores in post-stroke trial when compared to other groups. Panel B compares groups in 11 reaching components. Stroke + stress rats had significantly lower scores in grasp, supinations I and II, and release. Frames abcd show diminished grasp, supinations I and II, and release in a typical rat with stroke and stress. (Asterisks indicate significant difference: * P<0.05, ANOVA).
movements, as indicated in Fig. 5, upper panel. The largest deviation in body positioning was found in three out of 5 STROKE + STRESS animals, which was likely linked to the larger impairments in reaching movement performance.

Discussion

The morphological results of this study indicate that the intrastriatal injection of ET-1 was ischemic in nature, arguably, due to its prolonged and marked vasoconstrictive effects. Skilled reaching and spatial behaviors remained unaffected by either ventrolateral striatal focal ischemia alone or chronic stress alone. The combination of stroke and stress detrimentally influenced skilled limb use. Interestingly, neither the lesion volume nor spatial performance was affected by the synergistic effects of stroke and stress.

ET-1-induced stroke: applied aspects in animal studies

In animal stroke models, focal ischemia can be produced by ET-1, an endogenous potent and long-acting vasoconstricting peptide (Yanagisawa et al., 1988) injected directly into the brain tissue. Previous studies have established the usefulness of ET-1 for inducing focal ischemia in the forelimb motor region of the cortex (Windle et al., 2006), the dorsal frontoparietal cortex (Fuxe et al., 1997), the hippocampus (Mateffyova et al., 2006; Driscoll et al., 2008; Tsenov et al., 2007; McDonald et al., 2008; Spanswick et al., 2009; Faraji et al., 2011a), sensorimotor cortex (SMC; Adkins-Muir and Jones, 2003; Allred and Jones, 2004; Adkins et al., 2004), and striatum (Fuxe et al., 1992; Ottani et al., 2003; Windle et al., 2006; Peeling et al., 2006; Clarke et al., 2009). The stereotaxic intracerebral injection of ET-1 involves simpler surgical techniques with less post-surgical complications (Sharkey et al., 1993; Sharkey and Butcher, 1995). Because blood flow reduction in the ET-1 model of ischemic stroke is rapid, but not immediate (Macrae et al., 1993) and reperfusion occurs over several hours (Biernaskie et al., 2001; Macrae et al., 1993), this neuropathological profile may be more representative of human stroke than the immediate reduction and reperfusion seen with other animal models of ischemic stroke. Therefore, ischemia following ET-1 delivery resembles vital clinical aspects of vasospasm in the affected tissue.

Striatal lesions and behavioral consequences

Striatal stroke was chosen in the present study because the striatum is a key structure for integrating and relaying information in different modalities (e.g. sensorimotor, emotional, cognitive) from distributed areas of associative cortices, ultimately downstream motor areas (Alexander et al., 1986). Furthermore, as a sub-cortical site of the forebrain, this structure is critical in the pathophysiology of degenerative (Whishaw et al., 1986; Faraji and Metz, 2007; Eckart et al., 2010) and non-degenerative (Fuxe et al., 1992; Castañé et al., 2010) brain disorders. In this context, both cognitive and motor deficits have been reported after damage to the dorsal striatum in rats (Garside et al., 1996; Chang et al., 1999; Devan et al., 1999; MacLellan et al., 2006; Döbrössy and Dunnett, 2006; Haelewyn et al., 2007). While lesions in the dorsolateral striatum can disrupt sensorimotor function and simple stimulus response learning (Dunnett and Iversen, 1982; Reading et al., 1991; Yin, 2010), damage to the dorsomedial striatum has been shown to produce impairments in spatial cognition (Colombo et al., 1989; McGeorge and Faull, 1989).

Fig. 5. Frames showing four representative rats in sham, stroke-only, stress-only and stroke+stress groups in terms of their grasp, supinations I and II, and release in the single pellet reaching task. Small serial black and gray squares on the top of frames indicate the rats’ head and body posture, respectively, relative to the reaching slot.
In contrast to the anatomical results, the behavioral outcome, either motor or spatial, after unilateral focal lesion in ventrolateral striatum is poorly described. Stroke-only animals in our study showed no deficit in skilled reaching or spatial performance. The results not only confirm the functional heterogeneity within the neostriatum of the rats (Dunnett and Iversen, 1982; see also White, 2009 for review), they also indicate that the function of the ventrolateral striatum is not comparable to the adjacent dorsolateral striatum within which damage induces sensorimotor deterioration.

One of the unique features of the present results is the nature of focal structural damage. Because the ET-1-induced stroke was localized and restricted to the ventrolateral striatum, the behavioral outcomes reported in this study may reveal a better picture of the involvement of this sub-region of the neostriatum in skilled reaching behavior and spatial performance. Hence, the absence of sensorimotor and spatial deficit suggests a profile of striatal contribution in rats in which neither skilled limb use nor spatial performance critically depend on ventrolateral striatal circuitry.

Post-stroke functional outcomes induced by stress: precipitating or inhibitory effects?

It is generally believed that psychological stress is a critical influence on performance and disease (Sugo et al., 2002; Metz, 2007; Smith et al., 2008; McDonald et al., 2008). Our results showed that restraint stress had no impact upon the extent of the stroke-induced tissue loss. The similar structural consequences of restraint stress may represent an alternative picture of the involvement of the hypothalamic-pituitary-adrenal (HPA)-related outputs in the structural recovery after stroke when compared to previous reports (Casco et al., 2006; Smith et al., 2008; Kirkland et al., 2008; Zucchi et al., 2009; Jin et al., 2010). This discrepancy may be due to differences between the stress protocol, the model used for ischemic damage, and the location and extent of the lesions.

Stress-induced worsening of behavioral impairment, in the absence of any gross morphological changes following ventrolateral striatal stroke, highlights the effects of aversive experiences on functional improvement. Stroke + stress rats in the present study showed substantial movement deficits in the skilled reaching task starting from day six. This was reflected by both reduced reaching success and diminished movement scores. Both stress-only and stroke + stress groups also showed increased post-stroke attempts confirming previous reports (Metz et al., 2001, 2005) in which stress led to frantic reaching movements and reduced accuracy. Although the present examinations were based on a sensitive task of skilled movement, one may expect that synergistic effects of stress and stroke would also extend to other striatal motor functions (Cousins and Salamone, 1996a; Eagle et al., 1999; Tillerson et al., 2001).

Several mechanisms could account for the devastating behavioral consequences of post-stroke psychological stress. First, because stress is generally associated with high emotionality such as frustration, anxiety and fear (see Lupien et al., 2009 for review), stress-associated emotional changes may influence motor control. This may potentially uncover or precipitate motor dysfunctions, in particular those of delicate skilled movements.

Furthermore, stress may exert inhibitory effects in which normal responses (e.g. recovery and/or compensation processes) become suppressed. Any suppressive consequences of stress may obstruct behavioral recovery and/or behavioral compensation processes. One could assume that the reduced reaching performance after post-stroke day 6 may be caused by delayed inhibitory behavioral or pathophysiologic effects of restraint stress that prevents spontaneous motor improvement. In this context, both stress-induced impediment of compensatory limb use (deficits in compensatory adjustments) and suppressive effects of psychological stress on motivation or hedonic responses (Smith et al., 2008) should be considered.

Further support for the possibility of stress-associated motor disturbance is provided by the notion that the striatum, in addition to its involvement in goal-directed behaviors (Hollerman et al., 2000), serves as a crucial site for relaying stress information to forebrain structures (Robbins, 2005). One potential consequence of a focal damage of dorsal or ventral striatum in a stressed animal is likely a dysregulation in the central processing of stress-related information. Thus, striatal ischemic stroke and chronic restraint stress may exert synergistic effects on motor control that become noticeable in sensitive skilled movement tasks.

Concluding remarks

The synergy between focal stroke and stress on striatal motor control leads to a number of assumptions. First, stress may precipitate behavioral deficits after a focal ischemia or any vascular event that alone are not associated with observable functional deficits. This may become a key issue in particularly mini- or silent strokes where symptoms occur transiently or do not present clinically. Second, stress may inhibit the structural and/or behavioral mechanisms mediating functional improvement after focal ischemia. In this perspective, HPA axis activation possibly exerts suppressive effects on post-stroke recovery via glucocorticoid signaling as previously hypothesized (Sapolsky et al., 1986). Although it seems unjustified to define a stress state based on only HPA axis hyperactivity or elevated plasma CORT, more focus on related neuro-hormonal modulation of stroke recovery may provide new insights into the pathophysiology of motor dysfunctions after stroke and improved rehabilitation therapies. This knowledge can also help to identify therapeutic targets for stress-related complications after stroke.

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