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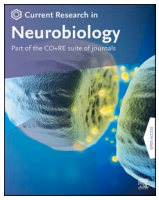

Longitudinal evaluation of the functional connectivity changes in the secondary somatosensory cortex (S2) of the monkey brain during acute stroke

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ABSTRACT

Background: Somatosensory deficits are frequently seen in acute stroke patients and may recover over time and affect functional outcome. However, the underlying mechanism of function recovery remains poorly understood. In the present study, progressive function alteration of the secondary somatosensory cortex (S2) and its relationship with regional perfusion and neurological outcome were examined using a monkey model of stroke.

Methods and materials: Rhesus monkeys (n = 4) were induced with permanent middle cerebral artery occlusion (pMCAo). Resting-state functional MRI, dynamic susceptibility contrast perfusion MRI, diffusion-weighted, T_1 and T_2 weighted images were collected before surgery and at 4–6, 48, and 96 h post stroke on a 3T scanner. Progressive changes of relative functional connectivity (FC), cerebral blood flow (CBF), and CBF/Tmax (Time to Maximum) of affected S2 regions were evaluated. Neurological deficits were assessed using the Spetzler approach.

Results: Ischemic lesion was evidently seen in the MCA territory including S2 in each monkey. Relative FC of injured S2 regions decreased substantially following stroke. Spetzler scores dropped substantially at 24 h post stroke but slightly recovered from Day 2 to Day 4. Relative FC progressively increased from 6 to 48 and 96 h post stroke and correlated significantly with relative CBFand CBF/Tmax changes.

Conclusion: The present study revealed the progressive alteration of function connectivity in S2 during acute stroke. The preliminary results suggested the function recovery might start couple days post occlusion and collateral circulation might play a key role in the recovery of somatosensory function after stroke insult. The relative function connectivity in S2 may provide additional information for prediction of functional outcome in stroke patients.

Introduction

Somatosensory deficits are frequently seen in acute stroke patients and may recover over time spontaneously and affect stroke outcome, but they are usually underestimated because motor symptoms raise greater awareness in the clinic and preclinical studies of stroke (Kessner et al., 2019; Kim and Choi-Kwon, 1996). A prior study of owl monkeys with WGA-HRP and fluorescent tracers indicated the primary motor cortex (M1) interacts directly with a few non-primary motor areas and somatosensory areas (Stepniewska et al., 1993). Also, it is demonstrated that the secondary somatosensory cortex (S2) is densely interconnected with the primary somatosensory cortex (S1) and parietal ventral area in the ipsilateral hemisphere and also with the S2 and S1 in the opposite hemisphere in a previous study of macaque monkeys to investigate how cortical fields process somatic inputs (Disbrow et al., 2003). A recent functional MRI study in patients suggested the sensory cortex (S1) is associated with motor learning and plays an essential role for post-stroke recovery (Frias et al., 2018). S2 is involved in the context of somatosensory dysfunction and sensory rehabilitation in stroke patients (Kessner et al., 2019; Lamp et al., 2018). However, the underlying mechanism of function recovery in the S2 following stroke insult remains poorly understood.

Rodent models of stroke have been widely used and play a critical role in neuroprotection research of stroke disease (Wang et al., 2015,

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2017; Jiang et al., 2012). In contrast, the stroke models of large animals like nonhuman primates (NHPs) shows superior advantage than rodents to improve the translational potential due to their similarities in brain anatomical structure, physiology, immunology, motor and somatosensory functionality with human and allowing for more extensive behavioral measures than rodents (Wu et al., 2016; Le Friec et al., 2021; Zhang et al., 2015; Cook et al., 2012; Roitberg et al., 2003). In addition, S2 in NHPs is recognized as a direct extrapolation of somatosensory cortex in human (Bretas et al., 2020). Therefore, NHPs are an ideal model in translational research of stroke and in particular, for investigating the functional alteration of the somatosensory cortex after stroke.

The resting state functional MRI (rsfMRI) technique has been popularly exploited for providing therapeutical information and quantitative measure of the brain functional impairment and recovery after stroke (Puig et al., 2018). In particular, animal models allow for longitudinal examination using fMRI (Silva et al., 2011). A previous study of stroke patients has demonstrated that the interhemispheric connectivity of S1 was associated with motor impairment (Frias et al., 2018). Also, it has been suggested the relative functional connectivity (Rel-FC) was a sensitive index to characterize the FC changes and in particular, allows for the comparison of connectivity across datasets from different MRI scanners due to its independent of image signal-to-noise ratio (SNR) compared to the traditional z-score measurement (Golestani and Goodyear, 2011). Also, the relative connectivity measures have been found to be a robust index to reveal the brain FC changes in a prior longitudinal study of stroke patients (Golestani et al., 2013).

In addition, cerebral blood flow (CBF) is thought to be a critical parameter to measure brain activity and functional recovery as it reflects the metabolic demands, neuronal viability and activity in the brain (Steiner et al., 2021). Also, regional CBF is coupled with resting fMRI-derived measures (Li et al., 2012) and higher CBF usually promote better recovery of cognitive functions in associated lesion regions post stroke (Boukrina et al., 2019). Perfusion MRI is a non-invasive alternative to measure CBF (Zhang and Li, 2016) and is gaining more interest in clinic study of stroke (De Vis et al., 2018; Yu et al., 2020). In particular, when regional CBF is immediately reduced after stroke insult, the injured tissue can become irreversibly damaged if CBF is below around 10 ml/100 g/min for 1–2 h (Baron, 2001).

The status of collateral circulation plays a critical role in sustaining tissue viability during acute ischemic stroke and determining function outcome and can also be examined using perfusion MRI (Okell et al., 2019). Tmax (time to maximum) is a perfusion index used to show hypoperfusion severity after stroke. Tmax and CBF maps both can show the hypoperfusion status of stroke-injured regions and are associated with an individual's collateral status (Lee et al., 2015). Thus, the CBF/Tmax volume ratio has been demonstrated to be an effective approach to differentiate between good and insufficient collateral circulation in acute ischemic stroke (Galinovic et al., 2018).

In the present study, we aimed to investigate the functional alteration of S2 in the brain following stroke insult and its relationship with collateral blood circulation and stroke outcome using a monkey model of stroke. Resting-state fMRI was utilized to examine the progressive changes of functional connectivity in S2 region following stroke, and CBF and CBF/Tmax would be performed to evaluate collateral circulation status in the brain after stroke insult.

Materials and methods

Stroke models and animal care

Permanent middle cerebral artery occlusion (pMCAo) was induced in the right hemisphere of healthy adult rhesus monkeys (n = 4, 10–19 years old, female) using the minimally invasive interventional approach reported previously (Zhang et al., 2015; Tong et al., 2015). The subject was initially anesthetized with 3–5 mg/kg of telazol and then intubated and maintained under 1.0–1.5% isoflurane anesthesia for the duration of the surgery (1–1.5 h). Once the distal M2 section of MCA was occluded and confirmed with the c-arm fluoroscopy (SIREMOBIL Compact, SIEMENS Medical Solutions USA, Inc.), the animal was prepared for transportation and immediately moved to the MRI suite under ketamine (15–30 mg/kg, i.v.) anesthesia for MR imaging. The subject was maintained under 1.0–1.5% isoflurane anesthesia for the duration of each MRI scan (3–6 h). After each MRI scan, the animal was recovered (except for the last scan) from anesthesia and housed individually (under 24-h video surveillance). The animals were watched closely in the first 24 h after surgery and routinely thereafter by the on-site vet staff and examined by a veterinarian daily. Also, animals were given softened chow, supplementary food treats (approved fruit, vegetables and nuts) and juice (to aid in the evaluation of swallowing difficulty and mild facial paresis). In addition, animals' attitude, appetite, stool, status and incision condition were daily monitored and recorded.

Also, the mean atrial pressure (MAP) and heart rate of the monkeys were maintained within normal ranges during each MRI scan session. No significant difference was seen in either MAP or heart rates between different time points post stroke.

MRI data acquisition

The rsfMRI, perfusion, diffusion-weighted, T_1 and T_2-weighted images were collected within one single scanning session before surgery (pre) and on 4–6 (Day 0), 48 (Day 2), and 96 h (Day 4) post stroke on a 3T scanner. Also, the axial images of rsfMRI, DWI, T_1, T_2, and perfusion MRI were aligned up with the AC-PC line during each monkey brain scan. rsfMRI data was collected using a gradient echo EPI sequence (TR/TE = 2190 ms/25ms, FOV = 96mm × 96 mm, data matrix = 64 × 64, 32 slices, voxel size = 1.5 × 1.5 × 1.5 mm^3 and 430 vol). T_2-weighted images were collected with a fast-spin echo sequence, and T_1 -weighted images were acquired with the 3D MPRAGE sequence for image co-registration and lesion region identification (Fig. 1). Dynamic susceptibility contrast (DSC) perfusion MRI was conducted with the bolus injection of Gd-DTPA (0.02 mg/kg, Ominiscan, GE Healthcare, USA) followed by a 20 ml saline flush) (Zhang et al., 2015). The DSC data were collected by using the EPI sequence with MRI parameters: TR/TE = 1540/20ms, FOV = 96 mm × 96 mm, data matrix = 64 × 64, 16 slices (to cover the whole lesion areas). In order to identify the infarction post stroke, diffusion-weighted images were collected with a single-shot EPI sequence with the parameters: TR = 5000 ms/TE = 80 ms, b-value = 0, 1000 s/mm^2, 30 gradient directions, 1.5 mm isotropic resolution.

Resting-state functional MRI

In the present monkey study with a small sample size (n = 4), we did not use a template of the monkey brain for co-registration because spatial normalization may reduce the detection sensitivity for fMRI study (Weng et al., 2015). Therefore, T_1 weighted images of each animal at each time point was co-registrated to the corresponding preprocessed EPI images (with field map correction, slice timing correction and rigid body registration) by AFNI script. Regions of interest (ROIs) of the contralesional (S2-Con) and ipsilesional (S2-Ipsi) S2 (Fig. 2A) were defined manually on EPI images based on the monkey brain atlas and corresponding T_1 weighted images. The time serial signal of EPI data in white matter and cerebrospinal fluid were regressed out with a general linear model using temporal filtering with 0.009 Hz–0.0237 Hz band-pass and spatial smooth by a Gaussian blur with 2.5-mm full width at half maximum) using a script from AFNI (http://afni.nimh.nih.gov). ROIs in each monkey were re-drawn at each time point.

The averaged time courses of the S2-Con were used as seed signals for seed-based correlation analyses (Fig. 2A) on the preprocessed EPI data to obtain correlation map. *Z* transformation was applied to normalize the correlation maps to functional connectivity (FC) maps. The FC maps from each monkey before surgery (pre) and on Day 0, Day 2, and Day 4 post stroke were aligned up and overlapped on a monkey

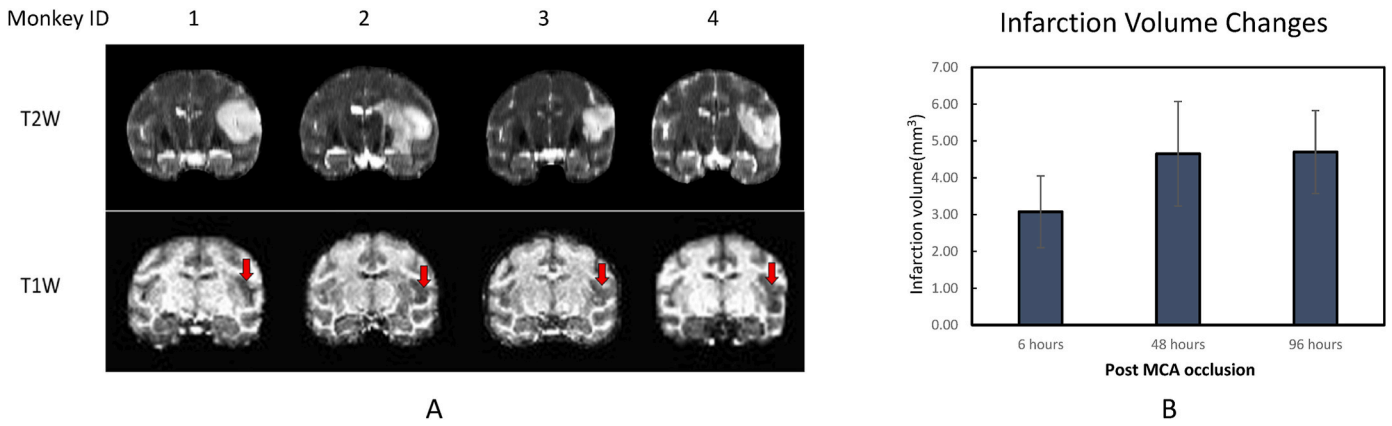

Fig. 1. Demonstration of infarction evolution in monkey brains. (A) Illustration of the representative slices of coronal T2 weighted images (T2W) (top) and corresponding T1 weighted images (T1W) (bottom) with cortical ischemic lesion including the second somatosensory cortex (S2) from 4 stroke monkey brains (1–4). The red arrows point to the ischemic lesion in S2. (B) Infarction volume changes following permanent middle cerebral artery (MCA) occlusion. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

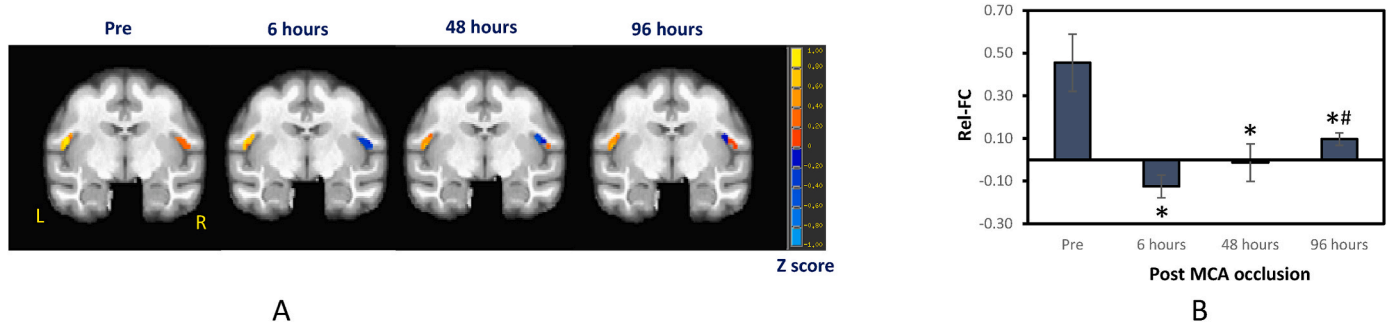

Fig. 2. Demonstration of functional connectivity alteration in the secondary somatosensory cortex (S2) of monkey brains following stroke. (A) Illustration of relative function connectivity (Rel-FC) changes in the stroke-injured S2 of a monkey in which the contralesional side (coronal view) was used as seed for functional connectivity analysis before stroke surgery (Pre) and at 6, 48, and 96 post stroke. $p = 0.026$ with 20 voxels as threshold. (B) Relative FC changes of S2 in monkey brains after MCA occlusion. *, $p < 0.05$ compared to Day 0 post stroke. Error bar indicates standard errors. Pre, pre scan before stroke surgery. $n = 4$. L and R indicate the left (control side) and right (lesion side) hemisphere respectively.

template for visual representation (Fig. 2A). In particular, the relative connectivity (Rel-FC) has been demonstrated to be more sensitive to detect reduced connectivity and was used in the FC result analysis (Golestani and Goodyear, 2011). Relative FC is defined by the formula: Rel-FC = FC-Ipsi/FC-Con. The FC maps across voxels within each ROI were averaged for every animal at each time point.

Perfusion MRI

Perfusion maps (CBF and Tmax maps) were generated from the original DSC data sets with the perfusion software package on a Siemens Workstation (Siemens Healthineers, USA). The similar ROIs of S2 used in fMRI data processing were drawn on corresponding CBF and Tmax maps with the software ImageJ but adjusted to exclude the odd pixels on CBF

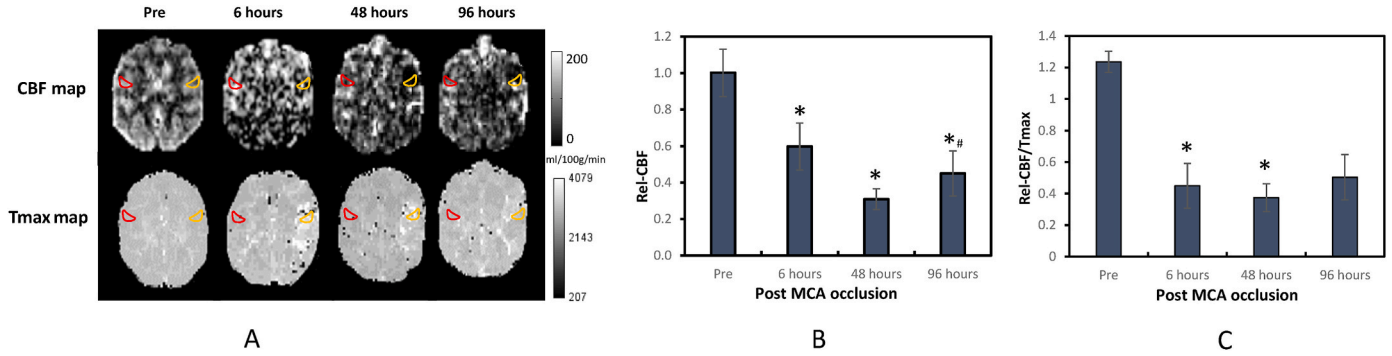

Fig. 3. Demonstration of CBF (cerebral blood flow) alteration in the secondary somatosensory cortex (S2) of monkey brains following stroke. (A) Illustration of axial CBF (top) maps and Time-to-Maximum (Tmax) maps (bottom) of a stroke monkey brain (closed red and orange curves mark the contralesional and ipsilesional regions of interest (ROIs) in S2. (B) Relative CBF (Rel-CBF) and C) relative CBF/Tmax (Rel-CBF/Tmax) changes in S2 of monkey brains after MCA occlusion. *, $p < 0.05$ compared to pre scan. Error bar indicates standard errors. Pre, pre scan before stroke surgery. L and R indicate the left (contralesional side) and right (ipsilesional side) hemisphere respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and Tmax maps. The averaged CBF with Tmax≥7s was estimated in the contralesional (CBF-Con, Tmax-Con) and ipsilesional (CBF-Ipsi, Tmax-Ipsi) S2 of the brain (Fig. 3). Relative CBF was derived by the formula: Rel-CBF = CBF-Ipsi/CBF-Con. Relative Tmax was derived by the formula: Rel-Tmax = Tmax-Ipsi/Tmax-Con. The relative CBF/Tmax was derived by the formula: Rel-CBF/Tmax = Rel-CBF/Rel-Tmax. The ROIs in each monkey brain were re-drawn for perfusion data analysis at each time point.

Lesion volume measurement

Lesion volumes were processed by using the DWI (Day 0) or T_2 weighted images (T_2w) (Day 2 and 4). DWI-derived volume was estimated using the threshold (mean + 2 × standard deviation (SD)) of the intensity on the contralateral side with home-built Matlab scripts. T_2w-derived lesion volumes were obtained using manually drawing by referring to T_2-weighted images of the contralateral hemisphere of the brain (Zhang et al., 2015). Lesion volumes were calculated as the sum of the lesion region in each slice multiplied by the slice thickness.

Neurological assessment

Neurologic assessment was conducted by an experienced veterinarian to examine the animals (and watch record videos also) before surgery (baseline) and post-stroke daily (24 h, 42 h, 72 h and 96 h post stroke). The assessment included three parts: 1) Motor function (10 points for Severe hemiparesis, 25 points Mild hemiparesis, 55 points Normal strength: Favors opposite extremity, 70 points for Normal strength: Normal function); 2) Behavior (0 points for Death, 1 points for Coma, 5 points for Aware of surroundings: Not active, 15 points for Aware of surroundings: Moves in response to examiner, 20 points for Normal aggression) and 3) Ocular and cranial nerve function (1 points for Facial movement: Paretic, 5 points for Facial movement: Normal, 1 points for Visual Field: Hemianoptic, 5 points for Visual Field: Normal) ranging from 1 to 100, 5 points for visual fields, and 5 points for cranial nerve function as described previously by Spetzler et al. (1980).

Statistical analysis

Statistical analysis was conducted using the software SPSS 27.0 (SPSS Inc, Chicago, IL, USA). A repeated analysis of variance (ANOVA) was carried out with pre and the post-occlusion time point (Days 0, 2, 4) followed by post hoc analysis with $p < 0.05$ as the significant threshold and LSD (Least significant difference). Sequential goodness of fit metatest (SGoF)correction (Carvajal-Rodriguez et al., 2009) was used to adjust the alpha threshold for multiple comparisons to determine the differences across prescan and the post-occlusion time points for Rel-FC, Rel-CBF, Rel-CBF/Tmax in S2, and neurological scores. Pearson correlation was applied between Rel-FC and Rel-CBF, Rel-CBF/Tmax and neurological scores of the monkeys post occlusion. SGoF correction was used to adjust the significant threshold of correlation analysis.

Histology and immunohistology

All animals were sacrificed immediately without recovery from anesthesia after their last MRI scans. The brains were harvested and immersed in 10% buffered formalin. The brains were then blocked and sectioned at 50 μm using a freezing microtome for rhesus monkey brains. Selected sections were processed with Fast blue and eosin (Fast blue &E) and Glial fibrillary acidic protein (GFAP) staining with standard protocols (FD NeuroTechnologies, Inc., Columbia, MD).

All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at Emory University in a facility accredited by Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) and in compliance with the Animal Welfare Act and the Public Health Service Policy on Humane Care and Use of Laboratory Animals.

Results

Infarction volumes

Cerebral infarction was observed in the MCA territory of the right hemisphere including the S2 region in each monkey (Fig. 1). Edema was seen in the infarction area of each stroke brain at 48 and 96 h post stroke (Fig. 1). The entire infarction volumes of the stroke monkeys increased substantially from Day 0 to Day 2 and remained stable from Day 2 to Day 4 (3.08 ± 1.94 ml (n = 4), 4.65 ± 2.85 ml (n = 4), 4.7 ± 2.25 ml (n = 3) at 6, 48, 96 h post stroke respectively).

Relative functional connectivity (Rel-FC) in S2

A repeated-measures ANOVA determined that Rel-FC in S2 differed significantly across the 4 time-points ($F(3, 6) = 10.054$, $p = 0.009$), indicating a significant effect of time on FC changes in S2 post stroke. The post hoc pairwise comparison using the LSD correction showed substantial reduction of Rel-FC in S2 immediately following stroke insult on Day 0 (compared to prescan, −0.13 ± 0.09 vs. 0.45 ± 0.23, $p = 0.063$, SGoF uncorrected). Significant decrease but progressive increase of Rel-FC was seen on Day 2 (compared to prescan, −0.01 ± 0.05 vs. 0.45 ± 0.23 $p = 0.036$, SGoF uncorrected) and Day 4 post stroke (Fig. 2A). The Rel-FC at Day 4 was significantly higher than that on Day 0 (0.10 ± 0.05 vs. −0.13 ± 0.09, $p = 0.029$, SGoF corrected) though it was still much lower than that at prescan (0.10 ± 0.05 vs. 0.45 ± 0.23, $p = 0.097$, SGoF uncorrected. Fig. 2B).

Relative cerebral blood flow (Rel-CBF) in S2

A repeated-measures ANOVA result showed that Rel-CBF in S2 differed significantly across the 4 time-points ($F(3, 6) = 24.047$, $p = 0.001$), suggesting the significant effect of time on CBF changes in S2 post stroke. The post hoc pairwise comparison using the LSD correction showed substantial reduction of Rel-CBF in S2 immediately following stroke insult on Day 0 (compared to prescan, 0.60 ± 0.22 vs. 1.00 ± 0.22, $p = 0.057$, SGoF uncorrected), continue to decrease and reach significance on Day 2 (compared to prescan, −0.31 ± 0.10 vs. 1.00 ± 0.22, $p = 0.024$, SGoF uncorrected) (Fig. 2A). The Rel-CBF at Day 4 was significantly lower than that in pre-surgery (0.45 ± 0.21 vs. 1.00 ± 0.22, $p = 0.037$, SGoF corrected) and on Day 2 (0.45 ± 0. vs. 0.60 ± 0.22, $p = 0.007$, SGoF uncorrected) (Fig. 2B).

Relative cerebral blood flow/Tmax (Rel-CBF/Tmax) in S2

A repeated-measures ANOVA determined that Rel-CBF/Tmax in S2 differed significantly across the 4 time-points ($F(3, 6) = 7.855$, $p = 0.017$), indicating a significant effect of time on CBF/Tmax changes in S2 post stroke. The post hoc pairwise comparison using the LSD correction showed that significant reduction of Rel- CBF/Tmax in S2 immediately following stroke insult on Day 0 (compared to prescan, 0.35 ± 0.25 vs. 1.20 ± 0.14, $p = 0.018$, SGoF corrected), and continued to decrease on Day 2 (compared to prescan, 0.44 ± 0.14 vs. 1.20 ± 0.13, $p = 0.028$, SGoF uncorrected) (Fig. 2A). Slight increase was seen on Day 4 (compared to Day 2, 0.44 ± 0.14 vs. 0.35 ± 0.25, SGoF uncorrected) but still much lower than that in prescan (0.44 ± 0.14 vs. 1.20 ± 0.14, $p = 0.99$, SGoF uncorrected).

Neurological scores

The four neurological scores were shown in Fig. 4. The Spetzler scores dropped substantially on Day 1 but slightly recovered from Day 2 to Day 4. The repeated-measures ANOVA determined that only the scores of motor function differed significantly across 4 time-points (F (3,

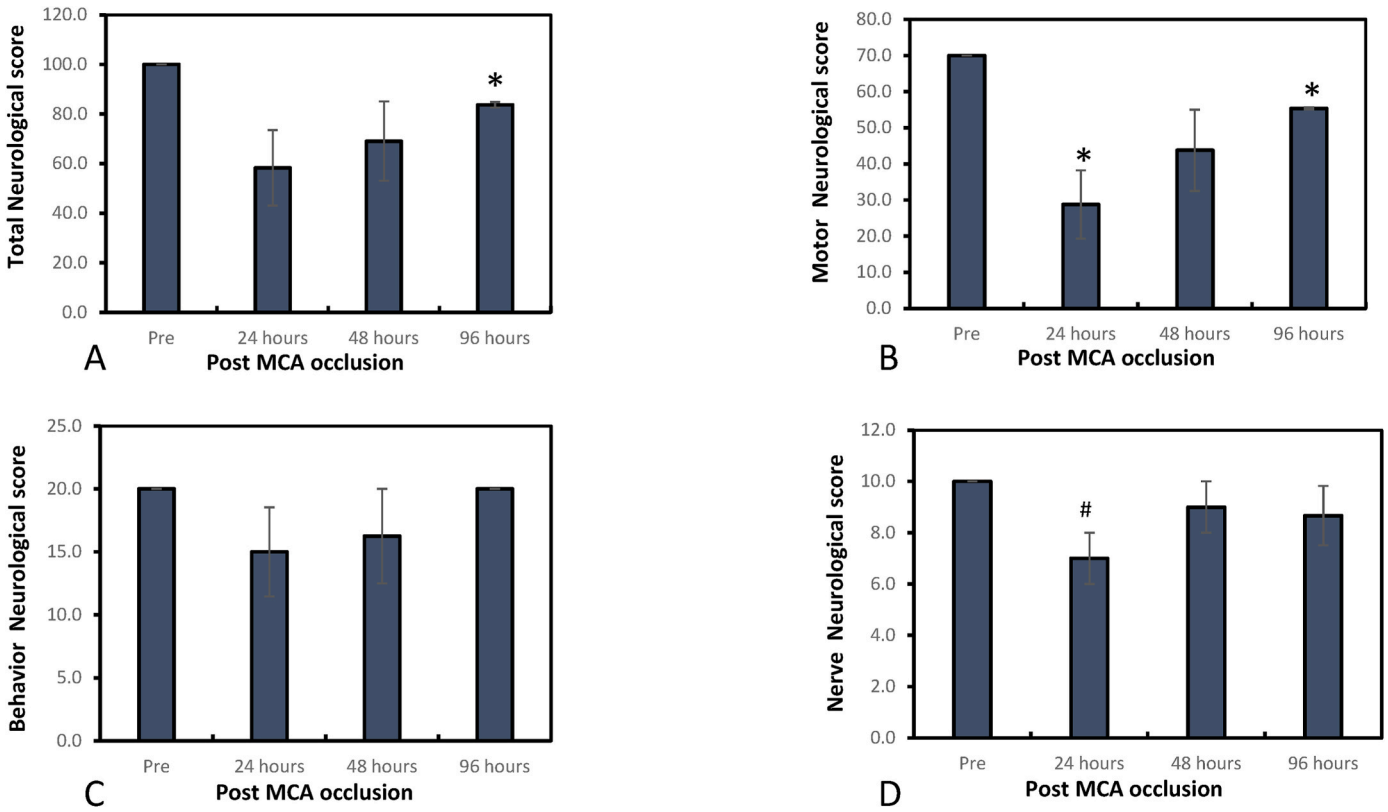

Fig. 4. Demonstration of neurological changes of the monkeys examined by the Spetzler approach after MCA occlusion. (A) Total neurological score; (B) motor neurological score; (C) behavior neurological score; (D) nerve neurological score. *, $p < 0.05$; compared to prescan. Error bar indicates standard errors. Analysis of variance (ANOVA) for repeated measures was performed to check the differences across different time points. Pre, prescan before MCA occlusion. n = 4 at pre, 24 h, 48 h; n = 3 at 96 h post MCA occlusion.

6) = 8.162, p = 0.015). The post hoc pairwise comparison using the LSD correction showed significant reduction of motor function on Day 4 (compared to prescan, 55.30 ± 0.58 vs. 70.00 ± 0.00, p = 0.001, SGoF uncorrected) even though slightly recovered at 48 and 96 h post stroke.

Overall, the temporal changes of CBF and Tmax maps in the S2 region of one monkey brain following ischemic stroke were illustrated in Fig. 3. Substantially decrease of Rel-CBF and Rel-CBF/Tmax in S2 were seen immediately after stroke surgery (6 h post stroke, p = 0.005, SGoF corrected). Substantial reduction of Rel-CBF and Rel-CBF/Tmax were seen at 48 h (p = 0.018, SGoF corrected) and slightly recovered at 96 h post stroke (Fig. 3B and C).

In addition, significant positive correlation was observed between Rel-FC and Rel-CBF (Fig. 5A, p = 0.025, uncorrected), between Rel-FC and Rel-CBF/Tmax (Fig. 5B, p = 0.023 SGoF corrected) of the brains from prescan to 96 h post occlusion.

In addition, the Fast blue & E and GFAP staining slices demonstrated the injured tissues in stroke monkey brains on Day 2 and Day 4 post stroke (Fig. 6). Obviously, neurons stained by Fast blue significantly decreased around the ipsilesional S2 post stroke while the glia cells illustrated by GFAP around the ipsilesional S2 region significantly increased compared to the contralesional S2 region.

Discussion

The preliminary rsfMRI results of stroke monkeys revealed substantial reduction in functional connectivity (FC) of S2 immediately following stroke and the slow but progressive increase of FC during acute stroke, indicating the spontaneous recovery process of S2 might

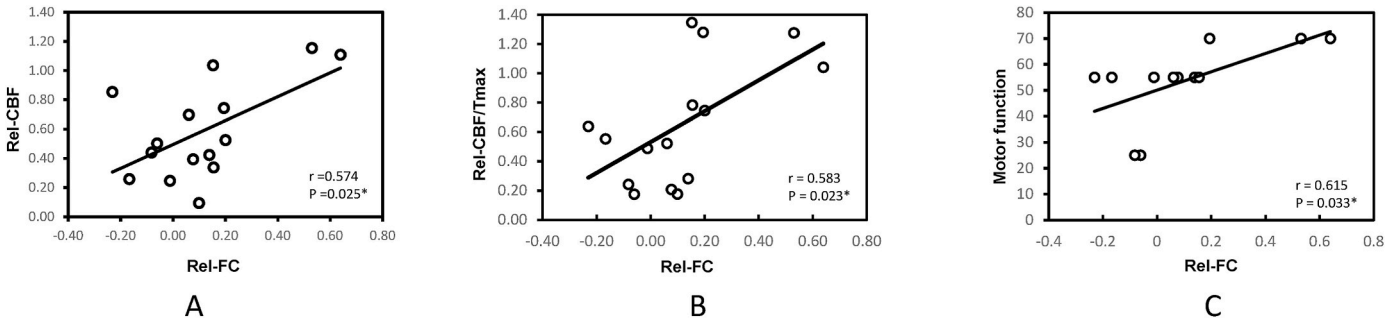

Fig. 5. Demonstration of the association of relative functional connectivity (Rel-FC) with regional CBF, CBF/Tmax and motor deficit following ischemic stroke. (A) The correlation between relative FC in S2 (Rel-FC) and relative CBF (Rel-CBF, n = 4) of stroke monkey brains from pre to 96 h post occlusion. (B) The correlation between the Rel-FC and relative CBF/Tmax (Rel-CBF/Tmax, n = 4) of stroke monkey brains from pre to 96 h post occlusion. #, p = 0.025, uncorrected; *, $p < 0.05$, SGoF corrected.

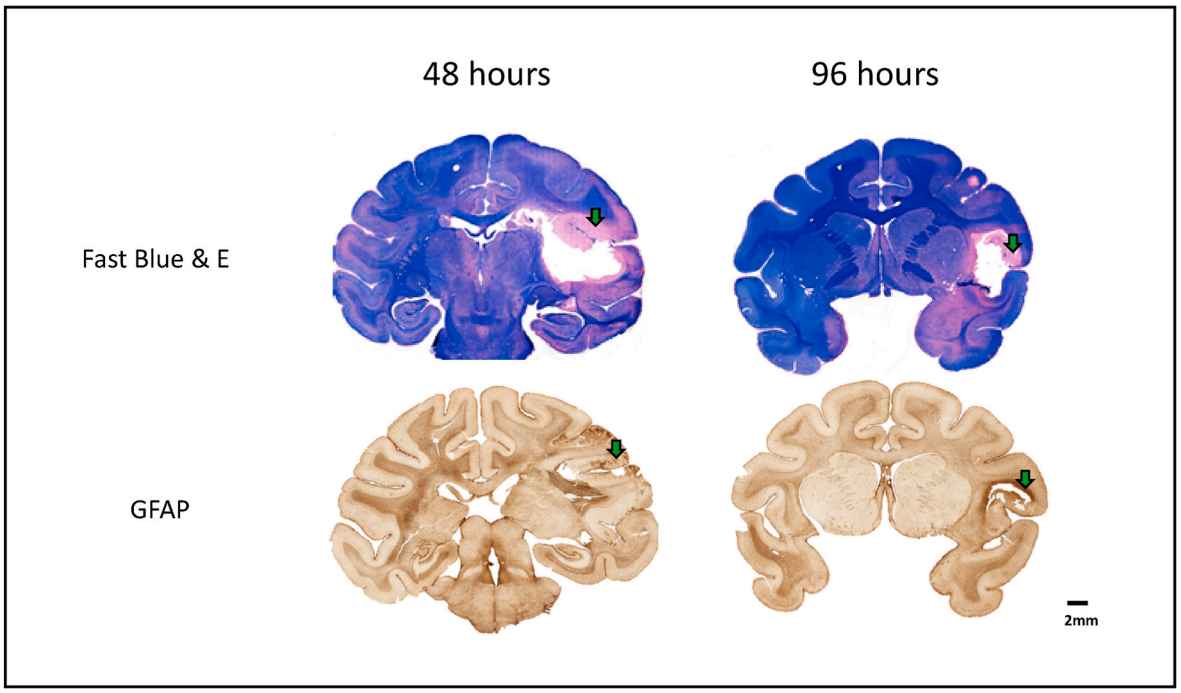

Fig. 6. Illustration of representative slides (coronal view) of Fast blue & E and GFAP staining of 2 monkey brains at 48 h and 96 h post stroke. The green arrows mark the injured area of second somatosensory cortex (S2) in monkey brains. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

start 48 h (or earlier) after stroke insult and the FC in S2 may be useful in prediction of stroke outcome. Also, the FC findings may partly explain how somatosensory deficits in stroke patients were recovered mostly within the first 3 months after stroke insult (Kessner et al., 2019). Furthermore, our results indicate the functional recovery in S2 during acute period is significantly relevant to regional CBF, suggesting collateral blood circulation may play a key role in the functional recovery of S2 post stroke.

Involvement of the somatosensory cortex in stroke

Somatosensory deficits are frequently seen in stroke patients (Kessner et al., 2019; Jang, 2013; Ingemanson et al., 2019), but have been generally underestimated as motor symptoms usually raise greater awareness in clinic studies (Kessner et al., 2019; Kim and Choi-Kwon, 1996). A previous rsfMRI study indicated the interhemispheric connectivity of primary sensory cortex (S1) were reduced after stroke injury and associated with stroke outcome of patients (Frias et al., 2018). The secondary somatosensory cortex (S2) is considered to play a critical role in light touch, pain, visceral sensation, tactile attention and object recognition and memory (Eickhoff et al., 2006), and known to involve the context of somatosensory dysfunction and sensory rehabilitation (Lamp et al., 2018). Clinical improvement in touch discrimination is related with increased interhemispheric function connectivity of S2 in chronic stroke patients (Bannister et al., 2015).

The S2 in the macaque monkey resemble that of human in neuroanatomy, and in particular, its response to somatosensory (Robinson and Burton, 1980), visual and auditory stimuli (Hihara et al., 2015). Therefore, the S2 in NHPs is considered as a direct extrapolation in the S2 specificity of human (Bretas et al., 2020). These stroke monkeys showed substantial infarction in the cortical area including S2 and allowed us to examine the effects of stroke injury on the function connectivity of the S2 region post stroke.

Functional connectivity changes in S2 during acute stroke

Functional connectivity (FC) has been used as a robust biomarker to quantify brain functionality alteration in stroke patients (Golestani et al., 2013) and anesthetized macaque monkeys (Meng et al., 2016; Zhao et al., 2018). Also, FC could be used to quantitatively assess the impact of stroke on the cognitive deficit of experimental animals and stroke patients (Puig et al., 2018), and showed the potential to facilitate the development of pharmaceutical therapies and to evaluate the efficacy of rehabilitation of stroke patients (Golestani et al., 2013).

Disrupted interhemispheric function connectivity in motor and sensory cortex is often seen in stroke patients as infarction is frequently appeared only in one hemisphere of the patients (Kessner et al., 2019). The alteration of the interhemispheric connectivity was usually examined to evaluate the motor skill damage in stroke patients (Li et al., 2016; Loubinoux et al., 2007) and associated with the sensorimotor deficit and behavioral improvement after stroke (O'Reilly et al., 2013). The disruption in the interhemispheric FC was also observed in stroke patients (Golestani et al., 2013; Carter et al., 2010), and in particular, in the S2, attention and motor networks of stroke patients (Goodin et al., 2018), suggesting it may be evaluated as a prominent characteristic in stroke patients. The relative connectivity (Rel-FC) is a robust measure of interhemispheric function connectivity and has been explored in a previous study of stroke patients (Frias et al., 2018). Accordingly, the approach was used here to investigate the interhemispheric dysfunction of the S2 in stroke monkeys.

Previous FC studies mostly focused on patients with chronic stroke, and reported that the recovery of FC in S2 was observed at 3 months (Goodin et al., 2018), 1–6 month period (Bannister et al., 2015) and 6-month period (Bannister et al., 2015) post stroke. The present monkey study revealed the progressive FC alteration in the S2 of monkeys during acute stroke, suggesting that the function recovery of S2 probably started just couple days post stroke.

CBF changes in S2 post stroke

MCAO results in focal brain ischemia and hypoperfusion is seen

immediately in the territory of MCA following the occlusion. In addition, the tissue fate is strongly depending upon the severity of hopyperfusion and timing of reperfusion or recanalization (Bardutzky et al., 2007). The reported CBF thresholds for penumbra and infarct core in clinical studies are 14.1–35.0 and 4.8–8.4 ml/100 g/minute, respectively (Lee et al., 2006). The mean CBF value in grey matter of rhesus monkey brains are about 104 ml/100 g/min (Zhang et al., 2007). As seen in the present report, the regional CBF in S2 of the monkey brains was 60 ± 22%, 31 ± 10%, 45 ± 21% of that in the contralesional S2 region at 6, 48, 96 h post stroke, respectively, indicating the S2 region was affected by the stroke but its CBF was still within the levels of benign oligemia and penumbra during acute stroke.

Also, the regional CBF (Rel-CBF) in stroke-injured brains of monkeys are temporally associated with function connectivity of S2 (Fig. 5C), in agreement with prior studies in children and adults with chronic stroke (Steiner et al., 2021; Richardson et al., 2011).The present results suggest the regional CBF changes are related with the recovery of cognitive deficit during acute stroke. In addition, the significant positive correlation between Rel-FC and Rel-CBF (Fig. 5A) suggested that FC is closely coupled with regional CBF during acute stroke and regional CBF plays a critical role in the functional recovery of S2 (Jann et al., 2015).

Effects of collateral circulation on S2 post stroke

Collateral circulation is a vascular network, maintaining the blood flow circulation in affected regions after blockage of vascular pathways (Vasquez et al., 2021). As the primary collateral circulation includes the individual arteries of the Circles of Willis and provides immediate diversion of CBF to ischemic regions, the polygon of Willis is considered as a most important source of collateral circulation (Vrselja et al., 2014; Konduri et al., 2020). Meanwhile, the secondary collaterals such as the leptomeningeal arterial anastomoses formed by MCA and anterior cerebral artery (ACA) and posterior cerebral artery (PCA), also play a key role to protect stroke injured tissues as they can provide compensatory blood flow to ischemic regions (Hung et al., 2022; Verma et al., 2015). However, high inter-individual variability in the number and size of the human leptomeningeal arteries were observed (Brozici et al., 2003), and several strategies can be applied to enhance collateral circulation of stroke patients (Bang et al., 2015).

Collateral circulation status plays a key factor in determining subsequent infarct growth so receive more attention in acute ischemic stroke (Lee et al., 2015) and is an important determinant of volume of cortical infarction (Seyman et al., 2016). A post-hoc analysis of Interventional Management of Stroke (IMS) III study revealed that the status of collateral circulation plays a key determinant of outcome of stroke (Liebeskind, 2014). Good collateral circulation is associated with a smaller infarct core in stroke patients (Rusanen et al., 2015; Nael et al., 2018).

Dynamic susceptibility contrast (DSC) and arterial spin labelling (ASL) perfusion MRI both have been used for the assessment of collateral circulation status (Galinovic et al., 2018; Tseng et al., 2020; Assadi et al., 2020). Time to maximum (Tmax) is a robust index to show hypoperfusion severity and widely used to evaluate collateral status independently (Lee et al., 2015; Guenego et al., 2020). Lee et al. analyzed data of patients who were eligible for recanalization therapy after acute ischemic stroke and found collateral circulation status was associated with Tmax delays, suggesting Tmax may be used to assess collateral circulation and subsequent infarct growth (Lee et al., 2015).

As a combined index, the CBF/Tmax ratio has been used to differentiate good and insufficient collateral circulation in patients of acute ischemic stroke (Galinovic et al., 2018). The present results revealed that the Rel-CBF/Tmax in S2 significantly decrease from 6 h to 48 h following stroke, and showed recovery trend at 96 h post stroke (Fig. 3B). The significant correlation between Rel-CBF/Tmax and Rel-FC in S2 revealed that the collateral condition contributed to the cognitive recovery post stroke. Also, the significant correlation between Rel-CBF/Tmax and Rel-FC ($r = 0.58$, $p = 0.023$, SGoF corrected) indicated the collateral circulation might contribute to the functional recovery in S2 following stroke by increased CBF supply in S2 area.

Infarction evolution and neurological evaluation

Diffusion weighted imaging (DWI) has demonstrated its specific sensitivity to detect very early infarct and its evolution following ischemic occlusion. Also, several mathematical models have been proposed to predict the infarction evolution during acute stroke (Wang et al., 2017; Zhang et al., 2015). As infarction is strongly associated with neurologic outcome, DWI images, T_1 and T_2 weighted images were collected in order to identify the ischemic infarction and territory at each time point.

The ischemic lesions in monkey brains at the 48 h post stroke were illustrated on the T_1 and T_2 weighted images as they have better spatial resolutions than DWI to show the lesion in the S2 regions (Fig. 1) (Zhang et al., 2015). The infarction volumes increased progressively from 6 to 48 h post stroke respectively but no obvious changes were seen from 48 to 96 h (4.65 ± 2.85 ml vs. 4.7 ± 2.25 ml), indicating the infarction was approaching their maximum volumes within these period (2–4 days) post stroke. Such finding is in agreement with a prior study of stroke patients in which maximum lesion volume was reached at around 74 h (or 3 days) post stroke and no significant further volumetric changes of ischemic lesion were seen on Day 4 (Lansberg et al., 2001).

As seen in the present monkey study, ischemic lesion was observed obviously in the S2 area of each monkey (Fig. 1). Edema was seen in the same regions at 48 and 96 h post stroke. The stroke lesion in S2 regions were further identified by histopathology staining (Fig. 6). The Fast blue &E results suggested that neurons and white matter both were injured in the lesion regions (Fig. 6). The GFAP staining showed increased GFAP positive cells around lesion in the stroke monkeys from Day 2 to Day 4. As GFAP is known as a best-identified marker of astrogliosis (Akhoundzadeh and Vakili, 2020), the increased GFAP positive cells might contribute to the functional recovery post stroke as reported previously in rodent models of stroke (Bilen et al., 2013; Otsuka et al., 2016). However, the positive or negative effect of astrogliosis after stroke is still in debate especially in early stage of stroke (Akhoundzadeh and Shafia, 2021).

The Spetzler neurological examination includes motor function, behavior, and ocular and cranial nerve function, and a total score is used to assess the neurological behavior change of NHPs post stroke (Spetzler et al., 1980). As demonstrated in Fig. 4, all scores decreased substantially on Day 1, compared to the pre-scan. The maximal decrease of motor function and nerve neurological scores was seen on Day 1 (Fig. 4), suggesting impact of ischemic lesion on the motor function during hyperacute phase of stroke. All scores showed function recovery on Day 3 and significantly improved on Day 5 post stroke when compared to the motor function score and total score on Day 1. As the Spetzler approach for neurological assessment is limited and can not specifically examine the S2 function deficit after stroke, more advanced behavior and neurological examination should be performed in NHP models to evaluate detailed function alteration of S2 in future studies of stroke.

Limitations

The effects of sex differences on stroke recovery were seen in patients (Gall et al., 2012; Gargano and Reeves, 2007), and female patients showed greater difficulty than the males in recovering. As rhesus monkeys are unique and limited resources, we could not find enough age-matched male monkeys at our facility, therefore only females were used in this study. The sex difference should be considered and examined in future studies. Also, the sample size was very limited in the present study. The reduction and progressive FC alteration in S2 were obviously observed but still couldn't pass the SGoF correction. The progressive FC alteration was just moderately correlated with local Rel-CBF and Rel-CBF/Tmax changes most likely due to the small sample size also.

In addition, monkeys are generally scanned under anesthesia. Isoflurane substantially suppresses the neural activation (FC) and increases the CBF in a dose-dependent manner (Zhang, 2022). Also, MRI scans could not be conducted daily in order to increase the power of study due to the concern about the animal care with frequently repeated anesthesia. Awake monkey fMRI studies have been used to examine ketamine-induced FC changes in the brain using a clinical 3T scanner (Gopinath et al., 2016) and may be used to assess the FC alteration in stroke monkeys in the future.

Conclusion

The present study of stroke monkeys revealed the temporal function connectivity changes during the spontaneous function recovery process of the secondary somatosensory cortex (S2) after ischemic injury and its association with regional perfusion during acute stroke. The preliminary results suggested the function recovery of S2 might start couple days post occlusion and be associated with the regional perfusion, indicating collateral circulation may play a critical role in the recovery of somatosensory function after stroke. As the primary and secondary cortex plays an essential role to process somatosensory inputs and affect stroke outcome, the relative function connectivity in S2 may provide additional information for prediction of stroke outcome in patients.

CRediT authorship contribution statement

Chun-Xia Li: Data curation, Investigation, Methodology, Writing – original draft. **Frank Tong:** Conceptualization, Investigation, Methodology. **Doty Kempf:** Data curation, Investigation, Methodology, Approval of final manuscript: all authors. **Leonard Howell:** Conceptualization, Investigation, Methodology, Supervision. **Xiaodong Zhang:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crneur.2023.100097.

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