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Cortical Reorganization Due to Impaired Cerebral Autoregulation in Individuals With Occlusive Processes of the Internal Carotid Artery

Jonathan List [a,b,*], Susan Hertel-Zens [a], Jan Carl Kübke [a], Anne Lesemann [a,b], Stephan J. Schreiber [a], Agnes Flöel [a,b,c,**]

[a] Department of Neurology, Charité-University Hospital, Berlin, Germany
[b] Center for Stroke Research Berlin, Charité-Universitätsmedizin Berlin, Germany
[c] NeuroCure Cluster of Excellence, Charité-Universitätsmedizin Berlin, Germany

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ABSTRACT

Background and purpose: To study the impact of impaired cerebral autoregulation on cortical neurophysiology, long term potentiation (LTP)-like plasticity, motor learning and brain structure.
Methods: 12 patients with unilateral occlusion or severe stenosis of the internal carotid artery were included. Impairment of cerebral autoregulation was determined by vasomotor reactivity in transcranial Doppler sonography. Corticomotor excitability, cortical silent period and LTP-like plasticity were assessed with transcranial magnetic stimulation, motor learning with a force production task, and brain structure with high-resolution MRI of the brain.
Results: In the affected hemisphere, corticomotor excitability was significantly higher, cortical silent period and LTP-like plasticity significantly lower, compared to the contralateral side. No significant difference emerged for motor learning, cortical thickness and white matter integrity between the hemispheres.
Conclusion: Despite decreased LTP-like plasticity in the affected hemisphere, motor learning was comparable between hemispheres, possibly due to gamma-aminobutyric-acid $(GABA)_B$-mediated corticomotor excitability changes within the affected hemisphere. Our results may help to develop interventions to beneficially modulate cortical physiology in the presence of cerebral hypoperfusion.

Introduction

Chronic cerebral hypoperfusion due to occlusive processes of the internal carotid artery (ICA) may induce subtle cognitive deficits including learning and memory formation, as noted upon neuropsychological testing [1]. Moreover, decline in motor function, such as gait disturbances have been associated with alterations in cerebral autoregulation [2].

Routine radiological examination of magnetic resonance imaging (MRI) does not reveal overt pathology in most cases, but reduced fractional anisotropy in diffusion weighted images and reduced functional connectivity in resting state functional MRI in the affected hemisphere (AH), as compared to the unaffected hemisphere (UH), have been reported [3]. On a cellular level, decreased long term potentiation (LTP) has been noted in animal models of hypoperfusion [5,6], a result corroborated by neurophysiological studies in humans using paired associative stimulation (PAS) in transcranial magnetic stimulation (TMS) to assess LTP-like plasticity within M1 [7]. PAS-induced LTP-like plasticity has been widely used as a model of Hebbian associative LTP [8] to study synaptic efficacy of the primary motor cortex (M1) in humans [9,10]. M1 also plays an important role in rapid motor learning and early consolidation of motor memories [4], possibly via LTP-like mechanisms [11,12].

Different TMS protocols have been used to explore cortical neurophysiology in various cognitive disorders, including Alzheimer's Dementia (AD) as well as vascular cognitive impairment

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* Corresponding author. Department of Neurology, Charité-University Hospital Charitéplatz 1, 10117 Berlin, Germany. Tel.: +49 30 450660223.
** Corresponding author. Department of Neurology, Charité-University Hospital Berlin Charitéplatz 1, 10117 Berlin, Germany. Tel.: +49 30 450660284.
E-mail addresses: Jonathan.List@charite.de (J. List), Agnes.Floeel@charite.de (A. Flöel).

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due to ischemic small vessel disease (SVD). Here, both patients with AD [13] and SVD [14,15] displayed higher corticomotor excitability, compared to healthy individuals. Turning to LTP-like plasticity, an interesting pattern emerged, with patients suffering from SVD but without clinical dementia demonstrating similar [16] or even enhanced [17] LTP-like plasticity, compared to controls, while patients with manifest dementia due to SVD [18] or AD [19] showed decreased LTP-like plasticity. Moreover, higher microstructural disease burden was associated with higher LTP-like plasticity in patients without dementia [20], suggesting that neurophysiological processes may play a compensatory role with regard to cognitive function.

So far, a comprehensive assessment of LTP-like plasticity and motor learning ability in both the AH and the UH, combined with detailed information on cerebral hemodynamic changes due to hypoperfusion, cortical neurophysiology, and gray and white matter structure has not been conducted in patients with steno-occlusive process of the ICA. However, such a study is needed to delineate mechanisms underlying preserved or impaired learning ability in individual patients.

Here, we aimed to comprehensively characterize changes in motor cortex physiology and motor learning in patients with impaired unilateral cerebral autoregulation. In 12 patients with unilateral steno-occlusive process of the ICA, cerebral autoregulation was assessed with transcranial Doppler sonography, structural integrity with cerebral MRI and subsequent analysis of cortical thickness and white matter integrity. We then evaluated motor learning ability using a force production task, and corticomotor excitability, GABAergic activity and LTP-like plasticity using TMS, in both the AH and the UH.

Methods

Subjects

We recruited 12 patients (aged 62 ± 14 years (mean ± SD), range 30–74 years, 3 women) with either unilateral high-grade stenosis of the ICA (>80%, ECST-criteria [21]; $n = 3$, all right sided stenosis) or unilateral ICA-occlusion ($n = 9$, 4 left sided occlusion) from the database of the ultrasound laboratory of the Department of Neurology of the Charité University Hospital in Berlin and the outpatient clinic of the Department of Neurology (Charité University Hospital) between August 2012 and December 2012. Patients with contralateral stenosis of the ICA (cut off ≥50%, ECST-criteria [21]) were not considered. All patients fulfilled the following inclusion criteria: 1) Diagnosis of occlusive process >1 year before inclusion to the actual study, 2) No transient or permanent neurological deficit within the last year, 3) Normal motor function on neurological examination, 4) No intake of medication that influence the central nervous system, 5) No signs of severe cognitive deficits (Mini Mental State Examination (MMSE) ≥ 26), 6) No signs of relevant depression (Beck's depression inventory (BDI) ≤ 12). Patients characteristics are provided in Table 1. 10 healthy older subjects (66.8 ± 5.9 years) participated in the pilot experiments.

All participants were right-handed according to the Edinburgh Handedness Inventory [22]. The study was approved by the local ethics committee in accordance with the declaration of Helsinki on the use of human subjects in experiments. Each participant gave written informed consent and received a small reimbursement after participation.

Experimental design

Pilot study

First, we conducted a pilot study to assess if hemispheric asymmetry (corresponding to dominant vs non-dominant hand) would confound respective TMS-measurements (LTP-like plasticity, resting motor threshold (rMT), and CSP) and motor learning in older individuals. TMS-measurements were obtained in 10 healthy older subjects bilaterally. The motor learning paradigm was tested in the same 10 healthy older subjects with the left and right hand.

Main study

In the main experiment, patients with unilateral stenosis of the ICA underwent a detailed clinical interview and a neurological examination including NIH-Stroke Scale, as well as neuropsychological testing. Extracranial color-coded sonography (ECCS) was carried out to confirm degree of stenosis. Impairment of cerebral hemodynamics was rated on both AH and UH using vasomotor reactivity (VMR) determined by transcranial Doppler sonography (see Transcranial Doppler sonography section). VMR assesses the compensatory potential of the brain blood-flow regulating vessels via providing a metabolic stimulus (CO_2). VMR is generally accepted as a major contributor in the concept of cerebral autoregulation and is particularly useful for determining the hemodynamic severity of carotid artery disease [23]. MRI were analyzed for structural

Table 1
Patients characteristics.

Patient	Age	Sex	Years of education	Risk factors	Side of stenosis/ occlusion	Degree of stenosis[a] (%)/occlusion	Etiology	Collateral activity	mRS	NIH-SS	Routine MRI examination
40	65	W	12	H, HLP	Right	80–90	Dissection	RACA, PCOA, LP	0	0	
43	63	M	17	H, HLP, DM	Right	90	Artherothrombotic	RACA, PCOA	0	0	
44	50	W	12.5	FMD	Right	Occlusion	Dissection	ROA, RACA, PCOA	0	0	
47	74	M	11	H, HLP	Left	Occlusion	Artherothrombotic	n.a.	0	0	ACA infarction left
48	30	M	14	–	Left	Occlusion	Dissection	RACA	0	0	
49	50	M	19	Smoking, HLP	Right	95	Artherothrombotic	RACA, PCOA, ROA, LP	0	0	
50	71	W	10	H	Left	Occlusion	Radiation-induced	RACA	0	0	
52	74	M	12	H, HLP, DM	Right	Occlusion	Artherothrombotic	RACA, ROA, PCOA	0	0	
53	53	M	10	H, HLP	Right	Occlusion	Artherothrombotic	PCOA	0	0	
55	74	M	12	H, HLP	Right	Occlusion	Artherothrombotic	RACA, ROA	0	0	Internal capsule infarction right (crus anterius)
51	55	M	16	H, HLP	Right	Occlusion	Artherothrombotic	RACA, ROA	0	0	ACA infarction right
56	80	M	18	H, DM	Left	Occlusion	Artherothrombotic	RACA, PCOA	0	0	

mRS = modified Rankin scale; NIH-SS=NIH Stroke Scale; MRI = magnetic resonance imaging; FMD = fibromuscular dysplasia; ACA = anterior cerebral artery; H = hypertension; HLP = hyperlipidemia; DM = diabetes mellitus; ROA = retrograde ophthalmic artery; RACA = retrograde A1 anterior cerebral artery; LP = leptomeningeal via PCA; PCOA = activated posterior communicating artery.

[a] Degree of stenosis was assessed by extracranial duplex sonography.

differences between hemispheres. We used FreeSurfer (https://surfer.nmr.mgh.harvard.edu) for cortical thickness analyses, and FSL (http://fsl.fmrib.ox.ac.uk/fsl) to analyze structural integrity of white matter fiber tracts. TMS was used to assess cortical neurophysiology, a force production task to assess motor learning (see Transcranial magnetic stimulation and Motor learning section) subsequently. For further details regarding MRI acquisition and analysis, see Supplementary methods.

Ultrasound

ECCS

ECCS was performed using a 7 MHz linear transducer (Toshiba Powervision 6000, Tokyo, Japan). The grade of internal carotid artery stenosis was assessed according to standard ultrasound protocols [24] and graded according to the ECST-criteria [21].

Transcranial Doppler sonography

Transcranial Doppler sonography was carried out in a quiet and darkish room to reduce visual and auditory stimuli in a comfortable lying position. Two TCD dual 2-MHz transducers were fitted on a commercially available headframe (DWL X4, Germany, Singen) and placed on the temporal bone windows. To assess VMR, mean flow velocity (MFV) was recorded over the middle cerebral artery (MCA) at rest (MFV-$MCA_{BASELINE}$) and after 2 min of carbogen-inhalation (5% CO_2 + 95% oxygen) (MFV-MCA_{CO2}). VMR was then obtained using the formula [25]:

$$VMR = (MFV - MCA_{CO2} - MFV - MCA_{BASELINE})/MFV - MCA_{BASELINE}$$

Patient #47 and Patient #56 had an insufficient temporal bone window, so VMR could not be assessed in these patients.

Transcranial magnetic stimulation

All TMS parameters were assessed bilaterally, with the investigator blinded to the hemisphere of the steno-occlusive process of the ICA. TMS thus consisted of two sessions, randomized between patients by a second investigator according to hemisphere of ICA stenosis/occlusion. Time interval between both sessions was at least 24 h.

TMS was delivered through a figure-of-eight shaped coil (9 cm outer diameter of each wing), which was connected to a Magstim 200 stimulator (Magstim, Whitland, Dyfed, UK). Participants seated comfortably in a reclining chair. The coil was held tangential to the scalp with the handle pointing backward at an angle of 45° to the interhemispheric fissure. The optimal position ("hot spot") of the coil was the cortical representation area of the abductor pollicis brevis (APB) muscle of the contralateral hand. On the "hot spot" a moderately suprathreshold stimulation intensity was leading to visible abduction of the thumb of the contralateral hand. The "hot spot" was then marked with a waterproof pen on the scalp of the subject. Motor evoked potentials (MEP) of the APB muscle were recorded via surface EMG activity using Ag/AgCl surface electrodes in a belly-tendon-montage. Raw MEP-signals were amplified and digitized and then stored on a laboratory computer for later offline analysis. The bandpass filter was 5 Hz to 5 kHz (Digitimer). Data were digitized at an analog-to-digital rate of 5 kHz.

Resting motor threshold

At the "hot spot," rMT was defined as the stimulus intensity (in % of maximum stimulator output) which was required to produce an MEP of the APB muscle of at least 50 μV in at least five of ten consecutive trials.

Cortical silent period

The cortical silent period (CSP) comprises both spinal (early phase) and cortical (late phase) inhibitory mechanisms [26]. The extended duration of the silent period, which is studied here, reflects the late phase, intracortical inhibitory mechanism that is thought to be mediated by $GABA_B$ receptors. Here, CSP duration was calculated at 2 TMS intensities separately for each hemisphere. Ten single-pulse stimulations for each of 2 TMS intensities (120% and 130% of rMT) were applied to the "hot spot." Participants maintained a voluntary isometric contraction of the respective APB at approximately 20% of their maximum strength by providing visual feedback from the surface EMG on a computer screen. Baseline CSP was obtained prior to MEP (1 mV) determination, which was in turn performed just before PAS.

PAS-induced LTP-like plasticity

A modified version of the PAS protocol first described by Stefan and colleagues [27] was administered [28] over the left and right hemisphere in two separate session at least 24 h apart. PAS consisted of an electrical stimulation of the median nerve at the wrist, followed by a subsequent TMS-impulse over the contralateral "hot-spot." According to the modified version of PAS, 132 paired stimuli were delivered at a frequency of 0.2 Hz. The interstimulus interval was set to 25 ms, which is known as the excitatory PAS-protocol [27]. Nerve stimulation was applied with a standard stimulation block (cathode proximal) with an intensity of 300% of the individual sensory threshold. TMS pulse intensity was set at 130% of rMT to evoke MEPs with a peak-to-peak amplitude of 0.5–1 mV in the relaxed APB. In order to maintain a standardized level of attention during the PAS intervention, subjects were instructed to stay alert, voluntarily relax the APB contralateral to the stimulated hemisphere, and count the number of median nerve stimulations. Muscle relaxation was continuously monitored by visual feedback from the surface EMG. The complete PAS protocol comprised baseline MEP measurements followed by the PAS stimulation and subsequent MEP measurements at time points 0 (T0, i.e., immediately after stimulation), 15 (T15), and 30 (T30) min after PAS. MEP amplitudes were measured peak to peak in each individual trial before and after intervention. For each time point, MEP were induced 10 times with a random pulse interval between 4 and 6 s. MEP amplitudes of each time point were then averaged and normalized to the MEP amplitude at baseline for each subject. LTP-like plasticity of each subject was then assessed by the grand average of normalized MEP amplitudes measured at time points T0, T15, and T30 [29].

Neuropsychological testing

We used a comprehensive neuropsychological test battery [30]. Processing speed and executive functions/set shifting were assessed with the trail-making-test [versions A.B], verbal fluency with the Regensburg Verbal Fluency Test (RWT, phonemic fluency with "S-words" and "G-R-words," and semantic fluency (simple fluency and category switching) with the categories "food" and "clothes-flowers"). The German version of the Auditory Verbal Learning Test was used to examine verbal learning capacity across five trials and the retrieval from verbal memory by delayed recall (30 min) (AVLT [31]). Digit span (part of the revised Wechsler Memory Scale [30]), forward and backward was performed to assess individual working memory performance. All results were compared to the percentile range of a normative group, matched for age and gender.

Motor learning

A motor learning task similar to the one previously described by Zeller and colleagues [9] was performed. Previous studies have

reported associations between this motor learning task and PAS-induced LTP-like plasticity [12]. In our slightly modified version, subjects had to perform 5 blocks of 30 consecutive brisk isometric abductions (0.25 Hz) with the thumb against a force transducer (Grass CP122A; Grass Instruments, West Warwick, RI) as close as possible to a defined target, which was set to 35% of the individual maximum force, to be followed on the computer screen. Each block was separated by 1 min. Motor performance was indexed by the averaged distance of each individual trial to the target in each block. Motor learning was assessed by the difference of the average distance at the beginning (Block 1) and at the end (Block 5) of the training.

Statistical analysis

LTP-like plasticity of each hemisphere was assessed by calculating the grand average of normalized MEP amplitudes measured at time point T0, T15 and T30 after PAS. To analyze influence of order (AH vs UH as first measurement) on LTP-like plasticity, a repeated measures analysis of variance ($ANOVA_{RM}$) with "hemisphere" as the repeated measure and "order of assessments" as a between subject factor was performed. Comparison in neurophysiological parameters between left and right hemisphere (pilot study) or UH and AH (main study) were evaluated by means of paired *t*-tests. Motor learning was assessed by the difference of the average distance at the beginning (Block 1) and at the end (Block 5) of the training. To quantify associations between structural MRI-parameters and neurophysiological parameters, we used, in an explorative approach, simple correlation analyses (CT vs rMT, CT vs LTP-like plasticity; CT vs CSP; CT vs motor learning; FA vs rMT, FA vs LTP-like plasticity; FA vs CSP; FA vs motor learning). Statistical analyses were performed using the statistical software R (www.r-project.org). Levels of statistical significance were set to $P < 0.05$, unless stated otherwise.

Results

Pilot study

Healthy older subjects showed a PAS-induced increase in motor cortex excitability (LTP-like plasticity) bilaterally, as expected. No differences in MEAN-LTP, rMT, or CSP were detected between right and left hemispheres (all *P*'s > 0.2; Fig. 1).

In the motor learning task, healthy subjects showed expected progress in motor accuracy, revealing highly significant improvement of accuracy between block 1 and block 5. The motor learning paradigm further did not show differences in left vs right hand (all *P*'s > 0.2) (Fig. 1).

Main study

Neuropsychological test results are provided in Table 2. In general, patients performed slightly below average in verbal learning, as indicated by the AVLT, compared with a percentile Rank of a normative group, in line with our own previous results [7]. VMR was severely decreased in the AH ($t = -5.58$; $P < 0.001$). No differences between AH and UH were found with regard to cortical thickness of the pre- or postcentral gyrus, gray and white matter volume as well as ventricular size, and integrity of white matter

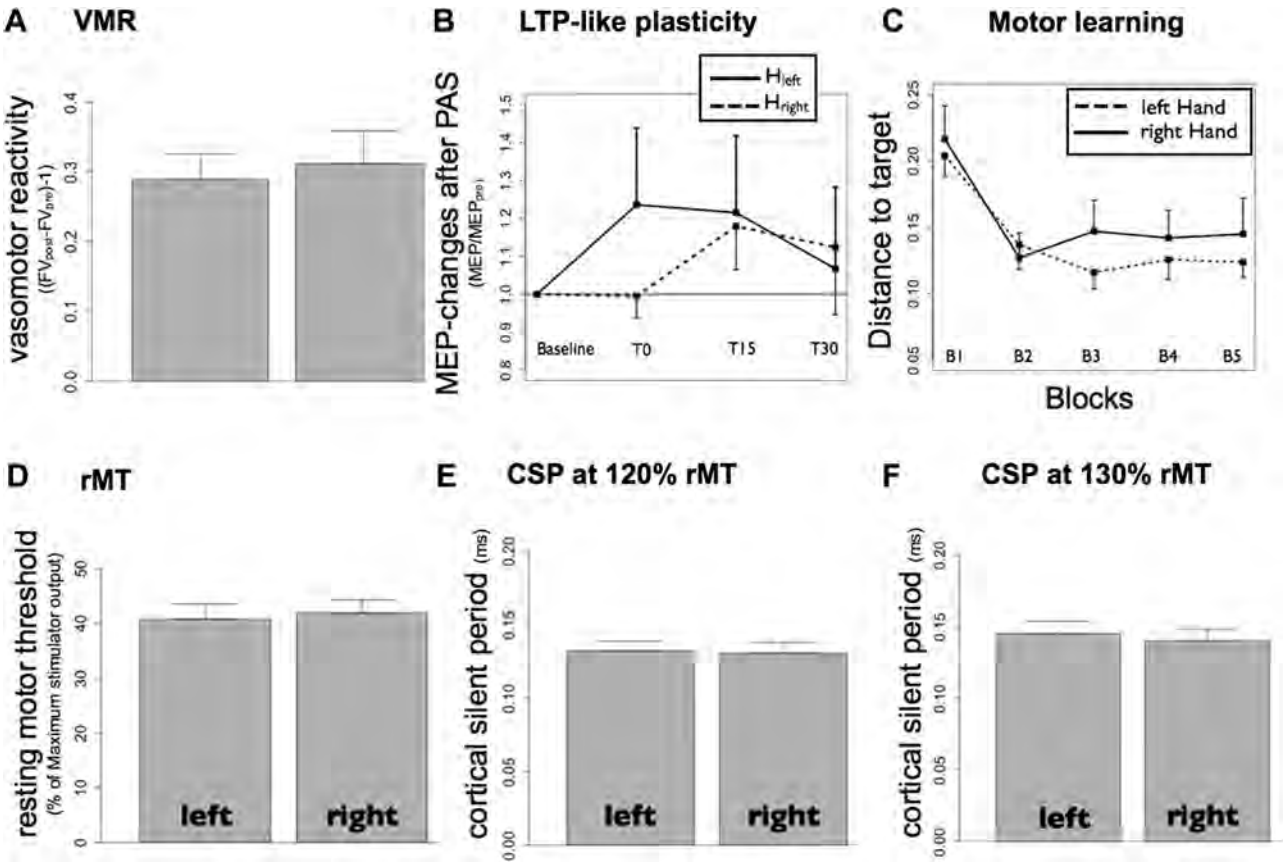

Figure 1. TMS-measurements in healthy subjects. MEP = motor evoked potential; PAS = paired associative stimulation; LTP = long term potentiation; rMT = resting motor threshold; CSP = cortical silent period. Error bars denote SEM.

Table 2
Age, MMSE, BDI and neuropsychological test results.

	Patients	Percentile range of normative group (%)
Age	62.33 ± 13.97	
MMSE	28.5 ± 0.90	
BDI	4.63 ± 2.67	
AVLT, sum 1–5	42.92 ± 8.77	30
AVLT, 7	8.08 ± 3.00	25
TMT-A	38.17 ± 13.02	>50
TMT-B	98.17 ± 36.31	50
RWT, S-words	18.67 ± 4.92	16–25
RWT, G/R-words	16.83 ± 4.55	10–16
RWT, food	28.33 ± 7.11	25–50
RWT, clothes-flowers	18.167 ± 5.02	16–25
Digit-span, forward	7.5 ± 2.15	35–57
Digit-span, backward	5.33 ± 1.83	12–30

MMSE = Mini Mental State Examination; BDI = Becks depression inventory; AVLT = auditory verbal learning task; TMT = trail making test; RWT = Regensburg word fluency task.

fiber tracts of the motor system, as determined by FA of the respective corticospinal tract (Table 3).

For LTP-like plasticity, $ANOVA_{RM}$ revealed no significant interaction of "hemisphere" × "order of assessments," but a significant main effect of "hemisphere" ($F = 8.775$, $P < 0.05$). Post-hoc paired *t*-test revealed a significantly lower LTP-like plasticity in the AH, as compared to the UH ($t = 2.67$, $P < 0.05$). Motor learning was comparable between hemispheres, as indicated by performance of the corresponding hands ($t = -0.39$, $P = 0.71$). rMT ($t = 3.67$, $P < 0.01$) and CSP at 120% rMT ($t = 2.39$, $P < 0.05$) were significantly lower in the AH when compared to the UH. CSP at 130% rMT was trendwise lower in the AH ($t = 2.22$, $P = 0.05$) (Fig. 2). No significant correlations were found between neurophysiological parameters and learning ability.

To assess possible confounding with regard to dominant versus non-dominant hand, we additionally compared motor performance for each block and motor learning, as well as LTP-like plasticity, rMT and CSPs as determined in the left versus right hemisphere, irrespective of stenosis/occlusion. No differences were found between left and right hemisphere for motor performance of each block (all *P*'s > 0.05), motor learning ($P = 0.5667$, $t = -0.5906$), LTP-like plasticity ($P = 0.22$, $t = 1.30$), rMT ($P = 0.62$, $t = 0.55$) and CSP at 120% rMT ($P = 0.81$, $t = 0.25$) and CSP at 130% rMT ($P = 0.66$, $t = 0.46$).

Comparison of neurophysiological findings of the AH in patients with healthy volunteers (pilot study)

LTP-like plasticity was significantly lower in the AH compared to the left and the right hemisphere in healthy volunteers. All other neurophysiological parameters were comparable between the AH in patients and both hemispheres in healthy volunteers, please refer to Table 4 for an overview.

Table 3
Structural MRI results.

	AH	UH	*t*	*P*
Lateral ventricle (mm^3)	17,363 ± 11,042	17,165 ± 10,961	0.288	0.779
Subcortical white matter volume (mm^3)	236,872 ± 28,213	236,900 ± 22,385	−0.0078	0.994
Cortex volume (mm^3)	215,571 ± 19,127	216,349 ± 14,250	−0.223	0.828
CT precentral gyrus (mm)	2.46 ± 0.227	2.51 ± 0.193	−0.915	0.400
CT postcentral gyrus (mm)	2.05 ± 0.095	2.09 ± 0.151	−1.013	0.333
FA CST	0.495 ± 0.014	0.503 ± 0.024	−0.908	0.384

CT = cortical thickness; FA = fractional anisotropy; CST = corticospinal tract; AH = affected hemisphere; UH = unaffected hemisphere.

Discussion

The main finding of the present study was that impaired cerebral autoregulation due to high grade stenosis or occlusion of the ICA in humans led to distinct changes in cortical physiology of the primary motor cortex in the absence of overt changes in brain structure and motor learning between the hemispheres.

Learning and memory are crucial in many activities of daily living. However, in the course of aging, these abilities may substantially decline [32,33], a process accelerated in SVD [34] or reduced cerebral autoregulation [35]. Motor function is in most cases not decreased in patients with impaired unilateral cerebral autoregulation but without manifest stroke [1]. However, transient behavioral symptoms as a consequence of transient focal hypoxia in patients with exhausted autoregulation and acute decrease in cerebral perfusion pressure, e.g., due to systemic hypotension, may occur [36,37]. In our patients, no intermittent neurological symptoms were reported, and motor learning was comparable between AH and UH, although LTP-like plasticity within M1 of the AH was decreased, even showing a trend toward long term depression. There is evidence, that M1 is specifically engaged during encoding of motor memories and in the early stage of motor consolidation [4], with LTP within M1 as the molecular basis of learning and memory formation [38]. Decreased LTP-like plasticity but preserved motor learning of the AH ability thus seems surprising at a first glance. However, a distinct neurophysiological pattern emerged in the AH, showing lower intracortical inhibition (ICI), as indicated by CSP, and higher corticomotor excitability, as indicated by rMT, in the UH.

CSP reflects ICI mediated predominantly by $GABA_B$ receptors [39], and is reduced or even absent after stroke induced lesions of the hand knob of M1 [40,41]. In patients with severe stenosis of the ICA, previous studies on CSP showed conflicting results: Murata and colleagues reported prolonged CSP in the AH [42], Katsoulas and colleagues shortened CSP in the AH [43], compared to healthy volunteers or to the contralateral hemisphere, respectively. Interestingly, the latter study reported a CSP increase after revascularization, indicating that hypoperfusion rather than structural lesions within motor areas may be the cause of CSP shortening in these patients. Since these studies did not assess LTP-like plasticity or motor learning, the impact of $GABA_B$-activity in these patients remained unclear. Other studies suggested higher presynaptic $GABA_B$ receptor activity to be associated with lower LTP-like plasticity and reduced motor learning [44]. In the present study, neither structural lesions within M1, nor higher $GABA_B$-receptor activity, as indicated by prolonged CSP were noted. Also we did not observe associations between CSP and LTP-like plasticity, or CSP and motor learning. Thus, low $GABA_B$-receptor activity and low LTP-like plasticity are most likely distinct sequelae of reduced cerebral autoregulation within the AH.

Additionally, we found an increase in corticomotor excitability of the AH, probably indicating adaptive functional reorganization of the motor system. For example, age-related thinning of M1 is associated with higher corticomotor excitability [20], and corticomotor excitability increases even further in patients with more pronounced M1 atrophy, such as AD [13] and SVD [14,15]. In these disease entities, dysregulation between inhibitory GABAergic and excitatory glutamatergic inputs have been demonstrated by TMS, possibly accounting at least in part for increased excitability (see Pennisi for review [45]). Higher cortical excitability and decreased

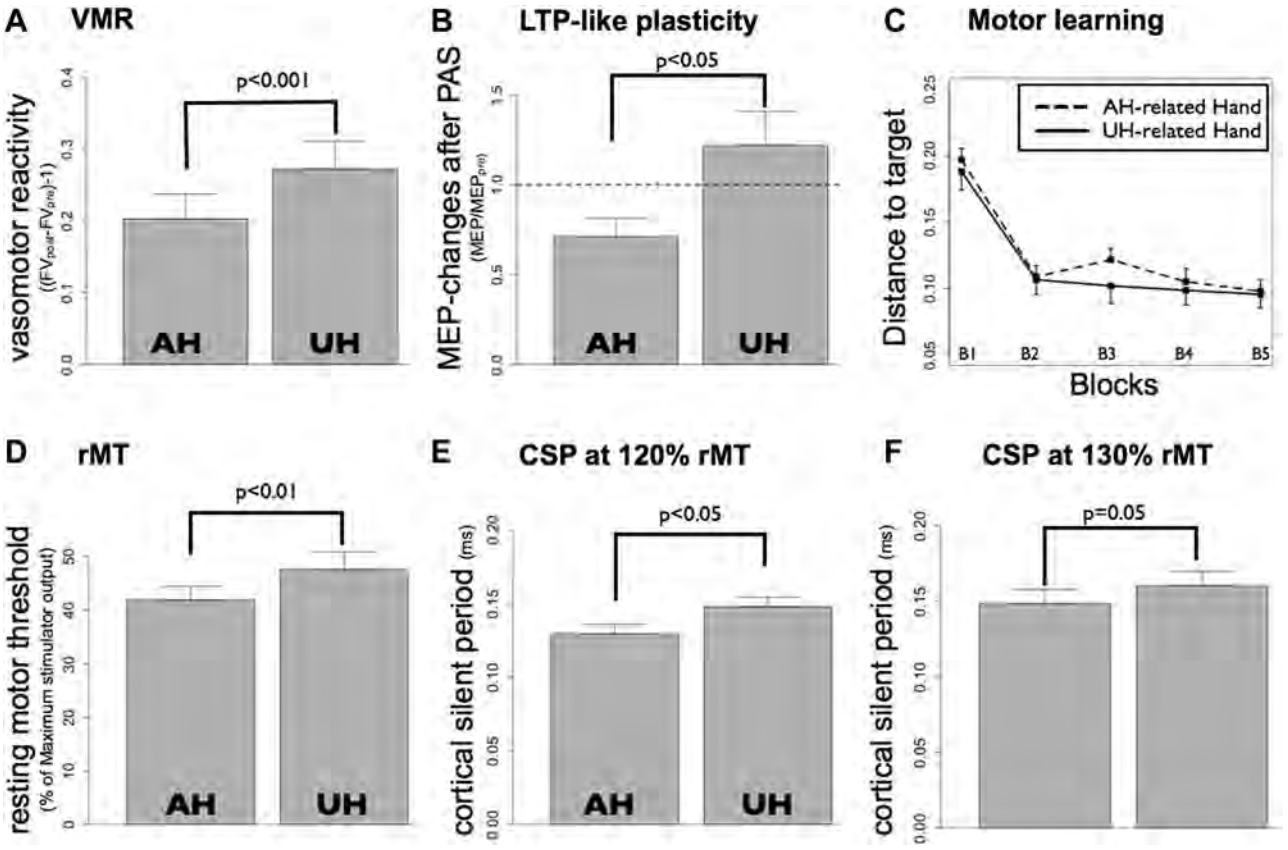

Figure 2. Neurophysiological and behavioral findings, comparing AH and UH. AH = affected hemisphere; UH = unaffected hemisphere; VMR = vasomotor reactivity; FV = flow velocity; LTP = long term potentiation; rMT = resting motor threshold; CSP = cortical silent period. Error bars denote SEM.

$GABA_B$-ergic inhibition might also be driven by ion-channel changes due to hypoxia. In fact, hypoxia has previously been shown to increase cortical excitability and decrease $GABA_B$-ergic activity in humans [46], similar to the changes indicated in our study by rMT and CSP. Thus, our findings on rMT and CSP in the AH could also be due to shifts in ion-concentration of cortical neurons in chronic hypoperfusion.

Interestingly, the decrease in $GABA_B$-mediated ICI was not reflected by higher or at least preserved LTP-like plasticity in the AH, as might have been hypothesized given previous findings that associated an increase in $GABA_B$-mediated ICI with decreased LTP-like plasticity [44]. Thus, our findings suggest that chronically impaired cerebral hemodynamics alter the ability to induce LTP-like plasticity, in line with previous studies on animal models of hypoperfusion [5,6], overriding any effect of reduced $GABA_B$-activity or increased corticomotor excitability on this type of plasticity. On the behavioral level, however, lower $GABA_B$-mediated ICI and higher corticomotor excitability may help to counteract the detrimental changes in LTP-like plasticity, as followed by decreased cerebral autoregulation.

Table 4
Comparison between affected hemisphere in patients and left and right hemisphere in healthy volunteers.

	AH (patients)	RH (healthy volunteers)	LH (healthy volunteers)		*t*	*P*
Neurophysiological parameters						
VMR (%)	20.27	31.17	28.89	RH	−1.83	0.08
				LH	−1.67	0.11
LTP-like plasticity (MEP [MEPpre])	0.698	1.099	1.214	RH	−3.06	0.008
				LH	2.07	0.06
rMT (%MSO)	41.91	41.89	40.75	RH	0.01	1
				LH	0.29	0.78
CSP120% (ms)	129	131	132	RH	−1.26	0.90
				LH	−0.26	0.80
CSP130% (ms)	146	140	145	RH	0.49	0.63
				LH	0.08	0.94
Motor learning						
Block 5—Block 1 (relative distance to target) (MEP [MEPpre])	−0.099	−0.088	−0.071	RH	0.50	0.63
				LH	1.51	0.16

AH = affected hemisphere; LH = left hemisphere; RH = right hemisphere; VMR = vasomotor reactivity; LTP = long-term potentiation; rMT = resting motor threshold; CSP = cortical silent period; MEP = motor evoked potential; MSO = maximum stimulator output; ms = milliseconds.

One limitation of the study is the rather small sample size and a wide age range between 31 and 80 years, possibly accounting for the fact that we did not find associations between motor learning and TMS-assessments. Furthermore our patient group was inhomogeneous in terms of side of stenosis/occlusion (right sided: $n = 8$, left sided: $n = 4$), although comparison of neurophysiological parameters of left and right hemisphere in healthy volunteers did not reveal differences between hemispheres. Strengths of the study include a comprehensive assessment of cortical autoregulation, brain structure and cortical neurophysiology of both hemispheres, and subsequent direct comparison of AH and UH, rendering age, diseases like general atherosclerosis, or environmental factors unlikely to interact with our present findings.

We believe that this study may help to better characterize functional and physiological adaptations of the cerebral cortex in response to chronic hypoperfusion. Understanding such adaptations is the basis to individually design non-invasive interventional studies, e.g., using transcranial direct current stimulation or repetitive TMS, to therapeutically modulate corticomotor excitability, intracortical inhibition [47] and cerebral hemodynamics [48,49].

Supplementary data

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