Brain Stimulation 7 (2014) 381–387

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

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

ARTICLE INFO

Article history:
Received 21 October 2013
Received in revised form
12 February 2014
Accepted 14 February 2014
Available online 20 March 2014

Keywords:
Carotid artery stenosis
Transcranial magnetic stimulation
LTP-like plasticity
Motor learning
GABA

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

Conflict of interest: None.
Funding: Deutsche Forschungsgemeinschaft (FI-379-8/1; FI-379-10/1; FI-379-11/1; DFG-Exc-257); Bundesministerium für Bildung und Forschung (FKZ0315673A; 01EO0801; 01GY1144); Else-Kröner Fresenius Stiftung (2009-141). J.L. is supported by the Clinical Scientist Program of the Charite Universitätsmedizin Berlin.
* 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).

1935-861X/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.brs.2014.02.006

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.