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ORIGINAL COMMUNICATION

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Motor cortex excitability in transient global amnesia

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Abstract *Objective* To investigate the physiology of motor cortical areas in patients with transient global amnesia (TGA). *Materials and methods* We performed transcranial magnetic stimulation (TMS) and single photon emission computed tomography (SPECT) in 13 patients during and after the acute phase of a typical episode of TGA. Measures of cortical excitability included motor threshold (MT) to magnetic stimulation, cortical silent period (SP) duration and intracortical inhibition (ICI) using a paired-pulse TMS technique. *Results* We found thalamic hypoperfusion and an ipsilateral significantly decreased ICI during the acute phase of TGA. *Conclusions* Reduced activity in inhibitory circuits may explain why PET studies of patients with TGA showed neocortical hypometabolism. Our findings are consistent with the hypothesis that frontal cortex dysfunction probably due to damage affecting the thalamocortical circuits may play an important role in the pathogenesis of the syndrome.

Key words transient global amnesia · transcranial magnetic stimulation · SPECT · PET

Introduction

Transient global amnesia (TGA) is characterized by isolated and transient anterograde amnesia of acute onset unaccompanied by disturbance of consciousness, focal neurological deficits or seizure, with uneventful follow-up in the vast majority of cases [6].

The pathophysiology of TGA remains unknown; there is uncertainly concerning the etiology, with a transient ischemia, a seizure and a migrainous phenomenon as most quoted mechanisms [10]. Even the localisation of neuronal dysfunction in TGA remains a matter for debate. There have been reports of unilateral infarctions of temporal lobes or thalamus in some patients who had suffered TGA, but the majority of the patients do not show permanent lesions on CT or MRI. TGA may be a core syndrome with several possible foci of dysfunction along the neuronal networks that subserve explicit memory.

Unilateral or bilateral significant diminution of regional blood flow in cortical areas, as detected by SPECT, has been recently reported during episodes of TGA. These changes affected mainly the frontal and/or lateral temporal cortex and were frequently associated with ipsilateral thalamic hypoperfusion [13, 25]; there have also been reports of neocortical-thalamic tandem hypoperfusion during episodes of TGA [9, 15]. It has been demonstrated that patients who exhibited the most marked cortical hypoperfusion also showed striatal and thalamic hypoperfusion [23].

Pathophysiological changes may therefore occur within the cerebral cortex, particularly in the motor areas which are a primary projection target of the basal ganglia.

Transcranial magnetic stimulation (TMS) is a noninvasive technique sensitive to changes in cortical excitability, which may serve as marker for relatively subtle changes in the physiological state of the brain and may therefore be helpful in evaluating thalamo-cortical modulation of the interneuronal activity in the cortex.

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The aim of the present study was to determine whether there are changes in the cortical excitability as measured by TMS during TGA and to correlate these findings with the functional imaging observations.

Material and methods

TSM together with a technetium-99m hexametylpropylamine oxime single photon emission computed tomography (Tc-HMPAO SPECT) of the brain were performed in 13 consecutive patients during and after the acute phase of TGA.

Patients

Thirteen patients (eight men, five women), aged 44–70 years and ten control subjects (six men, four women) aged 35–72 years, without prior history of cerebrovascular disorders, seizures, migraine or head injury, participated in the study.

The patients displayed the combination of complete anterograde amnesia, limited retrograde amnesia, incessant and repetitive questioning about his immediate circumstances typical for TGA and fulfilled all of the proposed criteria for that diagnosis [10]. They gave the same comment to the response, were unable to retain new information, remember public or personal events of the past year, to make appropriate responses about personal history during that time. The attack lasted between 4 and 13 hours with a mean duration of 6.4 hours.

Personality, semantic language, cognition involving high-level functioning, behavior were unremarkable; also problem solving and visuospatial ability were preserved.

Somatic neurological examination was completely normal in all patients.

The patients had no important change in the electroencephalogram, in particular no specific paroxysmal activity occurred. Brain CT showed no brain damage. Duplex ultrasound of the carotid arteries and echocardiogram were normal. The laboratory tests were unremarkable.

The neuropsychological assessment during the TGA episode showed intact short term memory, while long-term verbal and non verbal memory were severely affected in all patients. The neuropsychological 3 month-evaluation shows that the improvement of long-term memory was still not complete in 7 patients.

Neurophysiological procedures

We evaluated the following TMS parameters: a) the central motor conduction time (CMCT); b) the relaxed motor threshold (RMT) to magnetic stimulation; c) the duration of the cortical silent period (SP); d) the amount of the intracortical inhibition during paired magnetic stimulation.

Central motor conduction was evaluated using magnetic stimulation of the motor cortex and cervical spine through a 120 mm coil powered by a High-power Magstim 200 stimulator. Responses were recorded from the contralateral first dorsal interosseous (FDI) and tibialis anterior muscles. The CMCT was calculated by subtracting the peripheral conduction time from spinal cord to muscles from the latency of responses evoked by cortical stimulation [21]. The resting motor threshold (RMT) was defined as the minimum stimulus intensity that produced a liminal motor evoked response (about 50 γV in 50 % of 10 trials) at rest. The active motor threshold (AMT) was defined as the minimum stimulus intensity that produced a liminal motor evoked response (about 200 γV in 50 % of trials) during isometric contraction of the tested muscle at about 10 % maximum. A figure-of-eight coil (external loop diameter 90 mm) was used for stimulation. The induced current flowed in a postero-anterior direction.

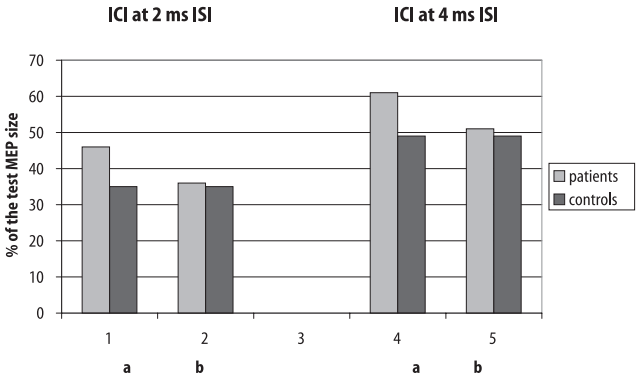

Fig. 1 Measures of intracortical inhibition (ICI) at interstimulus intervals (ISI) from 2 and 4 ms. During TGA (**a**) the patients (grey bars) have a reduced ICI compared with controls (black bars). $P < 0.05$. Means ± SD. After the acute phase of TGA (**b**) there were no significant differences

The silent period was elicited whilst subjects held a tonic contraction of approximately 50 % of the maximal voluntary contraction. Five stimuli at 150 % AMT were given.

The intracortical inhibition (ICI) was studied using the technique of paired magnetic stimulation with a subthreshold conditioning stimulus [11, 17]. Two magnetic stimuli were given through the same stimulating coil, using a Bistim module, over the motor cortex and the effect of the first (conditioning) stimulus on the second (test) stimulus was investigated. The conditioning stimulus was set at an intensity of 5 % (of stimulator output) below active treshold. The second test shock intensity was adjusted to evoke a muscle response in relaxed FDI with an amplitude of approximately 1 mV peak-to-peak. The timing of the conditioning shock was altered in relation to the test shock. Interstimulus intervals (ISIs) between 2 and 6 ms (intracortical inhibition) were investigated. Five stimuli were delivered at each ISI. Subjects was given audio-visual feedback at high gain to assist in maintaining complete relaxation. The amplitude of the conditioned response was expressed as percentage of the amplitude of the test MEPs.

Electrophysiological evaluation was performed during the acute phase of TGA and at least 3 days after the amnesic episode (only the measures of cortical excitability).

We performed also a Tc-HMPAO SPECT of the brain during and at least 3 days after the amnesic attacks.

Each patient underwent a neuropsychological assessment within 24 hours after the onset of the attack and retested 3 months later.

ANOVA (analysis of variance) was used to compare the cortical excitability measures. Results are considered significant if $P < 0.05$. The relation between different variables was evaluated by means of the Spearman's r correlation coefficient.

The study was approved by the institutional ethical committee. Prior to the investigation, patients and healthy volunteers gave their informed consent according to the Declaration of Helsinki.

Results

Electrophysiological data are summarized in the Table 1.

The CMCT was within the normal limits in all patients.

During the TGA attack ICI at interstimulus interval 2 and 4 ms was significantly reduced when compared with the control subjects (ANOVA, $P < 0.05$), whereas MT to

Table 1 Electrophysiological data of the patients with transient global amnesia and of the control subjects

Patients				CMCT Latency in ms FDI		CMCT Latency in ms Tibial. ant		Motor threshold (1)		Silent Period Latency in ms		Paired TMS (2) Interstim. intervals					
										2ms		4 ms		6 ms			
	G	A		L	R	L	R	L	R	L	R	L	R	L	R	L	R
1	M	61	a	7.5	7.4	16.2	16.5	55	60	164.0	168.4	31.2	33.5	31.8	45.6	94.2	95.3
			b					52	60	160.8	170.2	31.4	44.8	45.8	46.5	93.8	94.8
2	F	47	a	6.2	6.1	15.4	15.6	48	50	151.0	155.4	37.4	36.2	35.9	50.8	96.4	96.2
			b					50	50	155.4	156.8	35.5	52.5	46.3	50.5	92.4	97.5
3	M	65	a	6.5	6.3	14.8	15.0	50	52	172.2	175.0	32.8	34.1	32.3	47.0	89.2	90.6
			b					48	50	170.8	165.4	31.5	45.6	45.4	44.8	90.6	88.8
4	F	54	a	6.7	6.2	15.8	15.6	60	58	170.5	164.4	33.5	31.8	34.0	47.8	99.2	98.6
			b					55	55	160.8	158.6	33.7	48.5	45.8	45.5	96.8	94.7
5	F	48	a	6.4	6.2	14.5	14.7	58	55	152.5	151.0	34.5	36.8	33.1	50.5	97.2	99.0
			b					55	50	153.5	153.5	32.6	49.2	46.9	46.3	94.5	95.6
6	F	52	a	7.0	7.2	15.6	15.8	55	55	172.4	176.2	52.4	53.2	36.0	65.7	98.2	99.6
			b					55	58	168.9	172.3	35.9	64.2	49.7	50.3	92.6	98.8
7	M	51	a	6.8	6.2	15.8	15.4	52	55	170.2	173.0	57.7	55.6	37.8	74.8	100.4	98.6
			b					50	50	164.8	171.8	36.7	76.4	51.4	50.2	98.5	96.3
8	M	70	a	6.4	6.5	16.2	16.5	48	46	165.2	162.8	44.6	42.5	36.0	58.2	91.7	90.8
			b					45	47	164.5	153.5	36.3	58.8	52.5	52.6	90.5	89.5
9	F	44	a	6.1	6.3	15.6	15.7	60	62	180.0	183.5	56.2	57.1	36.8	75.7	97.7	98.5
			b					58	60	170.6	170.6	37.2	74.2	50.6	50.8	93.4	94.6
10	M	62	a	7.2	7.1	15.4	15.9	65	62	190.4	196.5	51.3	52.0	35.5	66.6	94.6	95.7
			b					62	60	188.6	186.7	35.8	65.4	51.2	51.4	92.6	93.2
11	M	59	a	6.8	7.0	16.2	16.4	58	60	172.6	175.0	54.2	55.7	36.8	72.4	99.1	99.8
			b					58	57	165.8	165.8	36.4	70.6	51.6	51.8	95.6	96.8
12	F	68	a	6.3	6.5	14.8	14.7	60	60	188.0	184.8	60.8	58.6	35.3	77.6	98.8	98.5
			b					62	58	180.6	186.5	35.0	78.4	51.4	51.2	96.7	95.4
13	M	67	a	6.4	6.2	15.8	16.0	65	68	172.8	180.2	47.4	46.8	36.5	61.3	96.4	96.2
			b					65	64	173.4	177.8	37.2	62.2	50.6	51.4	98.5	95.7
Control subjects																	
Mean				6.7		15.2		56		174.8		35.4		49.2		96.2	
Range				5.5–7.7		11.8–16.8		44–68		146.2–194.0		30.8–38.2		42.6–56.2		85.8–101.2	

L left; *R* right; *CMCT* central motor conduction time; *TMS* transcranial magnetic stimulation
(1) = Resting motor threshold expressed as percentage of the magnetic stimulator output
(2) = MEP amplitude after TMS at interstimulus intervals 2, 4 and 6 ms expressed as percentage of the main MEP amplitude obtained by a single TMS
a = during TGA; b = after the acute phase of TGA

magnetic stimulation (both relaxed and active) and the duration of the cortical SP showed no significant differences ($P > 0.05$). After the acute phase of TGA no significant differences could be observed regarding all neurophysiological parameters ($P > 0.05$).

No correlation was found between the age of patients and the neurophysiological abnormalities ($p > 0.10$; Spearman's r).

SPECT showed thalamic and striatal hypoperfusion in all patients, associated with unilateral or bilateral hypoperfusion of the temporal region in 4 patients and with variable hypoperfusion of further cortical areas in other 3 patients during the acute phase.

After the acute phase thalamic hypoperfusion was observed in 2 patients, with associated temporal hypoperfusion in one case.

Discussion

Our neurophysiological data indicate that it is possible to demonstrate changes in motor cortex excitability in patients with TGA. The principal finding is a pronounced reduction in the extent of intracortical inhibition during the acute phase. These results point to an impaired balance between inhibitory and excitatory intracortical circuitry. Apart from intracortical and intracallosal connections, the afferent modulation of the

motor cortex is mainly due to thalamocortical influences [5]. The cortical abnormalities could be therefore caused by deafferentation due to thalamic damage; the thalamus may represent the primary site of neuronal derangement. A reduced effectiveness of intracortical inhibitory mechanisms has also been previously reported in a patient with a lesion in the postero-lateral thalamus [16] and in patients with abnormalities in the basal ganglia-ventrolateral thalamus-frontal cortex loop [3, 20].

The finding of a reduced activity in the inhibitory circuits also supports the functional imaging observations from positron emission tomography (PET); a matched reduction in cerebral blood flow and oxygen consumption over the lateral frontal cortex on the right side has been described [2], with an associated reduction in ipsilateral thalamic and lentiform nucleus metabolism. These changes suggest right prefrontal metabolic depression, likely secondary to thalamic dysfunction, as the possible underlying mechanism for TGA. Moreover, neocortical hypometabolism is often found in patients with memory impairment and uni- or bilateral thalamic lesions [4, 14, 19], whereas it is absent in patients with pure internal capsular infarct [18].

Damage to the thalamus or the thalamocortical projections is therefore important in the development of ipsilateral cortical hypometabolism and the latter may underlie the associated neuropsychological impairment. The location of thalamic lesions is thought to be a major determinant of the ipsilateral cortical hypometabolism characteristic of cognitively impaired patients with thalamic lesions. In particular several reports emphatize the influence of the "non-specific" thalamocortical system on resting cortical metabolism [1, 22]; on the contrary ipsilateral cortical metabolism is not found in postero-lateral thalamic stroke [7]; the cortical hypometabolism could therefore reflect thalamo-cortical deafferentation secondary to damage to the "non-specific" thalamic nuclei.

However, most PET studies have failed to demonstrate a differential effect of different thalamic lesions; in fact small thalamic lesions result in extended cortical reduction of metabolism which far exceed the specific projection area of the focal lesions [12, 24]. Ischemic thalamic lesions are not restricted to individual thalamic nuclei or functional regions, because of both the very small size of the nuclei and their variable vascular supply not confined to a definite region; even the smallest ischemic region will affect intrathalamic fibers [5, 24]. Moreover, as in the monkey, each thalamic nucleus includes several separate populations of neurons that projected to different cortical areas and each area of sensorimotor cortex received input from several thalamic nuclei [8].

It remains unclear whether hypoperfusion represents a primary event or is a sequel of brain regional hypometabolism; furthermore, thalamic flow reduction itself could be caused by thalamic dysfunction of nonvascular etiology.

The ICI abnormalities may represent the electrophysiological correlate of the hypometabolism and hypoperfusion detected by PET and SPECT respectively.

This study provides the first direct evidence that the behavior of a specific cortical network, i. e. the system of excitatory afferents and inhibitory interneurons that is believed to regulate the excitability of corticospinal neurones, varies in the acute phase of TGA.

In conclusion our data, taken together with that from functional images studies contribute to the view that the origin of the TGA function changes lies at the level of the basal ganglia structures that project to the cerebral cortex; in particular the clinical manifestations might partly arise from motor cortex disinhibition.

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