Original Research

Corticospinal excitability in patients with anoxic, traumatic, and non-traumatic diffuse brain injury

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ABSTRACT

Background: Transcranial magnetic stimulation (TMS) have been frequently used to explore changes in motor cortex excitability in stroke and traumatic brain injury, while the extent of motor cortex reorganization in patients with diffuse non-traumatic brain injury remains largely unknown.
Objective/hypothesis: It was hypothesized that the motor cortex excitability would be decreased and would correlate to the severity of brain injury and level of functioning in patients with anoxic, traumatic, and non-traumatic diffuse brain injury.
Methods: TMS was applied to primary motor cortices of 19 patients with brain injury (5 traumatic and 14 non-traumatic causes; on average four months after insult), and 9 healthy controls. The test parameters included resting motor threshold (RMT), short intracortical inhibition (SICI), intracortical facilitation (ICF), and short latency afferent inhibition (SAI). Excitability parameters were correlated to the severity of brain injury measured with Glasgow Coma Scale and the level of functioning assessed using the Ranchos Los Amigos Levels of Cognitive Functioning Assessment Scale and Functional Independence Measure.
Results: The patient group revealed a significantly decreased SICI and SAI compared to healthy controls with the amount of SICI correlated significantly to the severity of brain injury. Other electrophysiological parameters did not differ between the groups and did not exhibit any significant relationship with clinical functional scores.
Conclusions: The present study demonstrated the impairment of the cortical inhibitory circuits in patients with brain injury of traumatic and non-traumatic aetiology. Moreover, the significant correlation was found between the amount of SICI and the severity of brain injury.

Introduction

Severe brain injury is a growing public health challenge [1]. The great heterogeneity of pathophysiological mechanisms that comprise the spectrum of diffuse and focal brain injuries requires a combined approach to electrophysiological assessment of brain function in these challenging patients. Somatosensory evoked potentials (SEPs) are widely used for evaluation of sensory pathways and outcome prognosis in severe brain injury, although the prognostic value of SEPs is highly dependent on aetiology of injury [2,3]. During the last two decades, motor evoked potentials (MEPs) following single-pulse or paired-pulse transcranial magnetic stimulation (TMS) have become an objective means for the assessment of motor cortex excitability and the integrity of motor pathways [4]. Application of single-pulse TMS in comatose patients might improve the assessment of motor dysfunction, but have no prognostic value for the long-term outcome [5]. Several studies indicate that cortical injuries, independent of their aetiology, can lead to a reduced strength of inhibitory neurotransmission [6–8]. The lesion-induced abnormal cortical excitability has been reported in the affected [6,7,9] and unaffected hemisphere [10,11] in patients with stroke. Cortical excitability, assessed using paired-pulse TMS, is shown to correlate with the severity of brain damage in patients with diffuse traumatic brain injury (TBI) [12–16]. Paired TMS has been proposed as a tool for predicting outcome after stroke [17] as well as predicting functional outcome after rehabilitation interventions [18]. Normalization of amplitude and waveform of MEPs

and motor threshold (MT) was related to the clinical recovery in mild to moderate TBI [19]. Despite this, studies identifying changes in cortical excitability in patients with diffuse non-traumatic brain injury due to subarachnoid haemorrhage and anoxia are rare, and the extent of motor cortical reorganization in these patients remains largely unknown. Moreover, we wanted to assess the relationship between paired TMS measures in the motor cortex and the clinical measures of the overall functional status and the level of consciousness. In order to test the excitability in the motor cortex, we studied (1) Resting motor threshold (RMT), as a measure of membrane excitability and anatomical features related to cortico-spinal tract function [20]; (2) Intracortical inhibition (SICI) and facilitation (ICF), as a measure of cortical inhibitory network depended on GABAA receptor activity [21,22]; and (3) Short latency afferent inhibition (SAI) [23,24], as a cortical inhibitory phenomenon thought to be regulated by cholinergic circuits [25].

Hypothesis

It was hypothesized that the motor cortex excitability would be decreased and would correlate to the severity of brain injury and level of functioning in patients with anoxic, traumatic, and non-traumatic diffuse brain injury.

Methods

Patients and controls

Nineteen patients with severe brain injury (trauma, $n = 5$; anoxic-ischaemic encephalopathy, $n = 3$; subarachnoidal haemorrhage, $n = 10$; infection, $n = 1$; 8 males; mean age (SD): 50.5 years [12]; mean time since injury (SD): 4.4 months (2.6), and nine healthy volunteers (5 males; mean age SD: 49.6 years [18]) were tested. Patients were recruited from Hammel Neurorehabilitation and Research Centre in Denmark. Inclusion criteria were: brain injury due to trauma, cardiac arrest, subarachnoidal haemorrhage or infection, which required intensive multidisciplinary inpatient rehabilitation due to moderate to severe cognitive impairment and/or motor deficit bilaterally after discharge from the acute hospital. Exclusion criteria were: history of other neurological or psychiatric diseases, alcohol or drug abuse, presence of other major medical illness. Patients were examined with computed tomography and/or magnetic resonance imaging during the hospitalization, time between neuroimaging and TMS examination was on average 1.9 ± 1.9 months after injury. All patients were scanned on the admission to the acute hospital and neuroimaging examination was afterwards repeated individually and determined by clinical needs. The following morphological diagnoses were made according to neuroimaging evaluation: no pathological funds (16%), focal lesion (79%), subarachnoid haemorrhage (58%), diffuse axonal injury (21%), hydrocephalus (37%); 84% of patients had more than one pathology. No sedative medication was administered prior to the TMS measurements. Eight patients were treated without neuroactive drugs, nine patients with one neuroactive drug (e.g. serotonin reuptake inhibitors ($n = 2$), adrenergic receptor inhibitors NaSSA ($n = 5$), and methylphenidate ($n = 2$)), and two patients with combination of valproic acid and clonazepam ($n = 2$). Demographic and clinical patient characteristics are summarized in Table 1. All participants were screened in order to ensure they weren't contraindicated to TMS [26]. This study was approved by the Central Denmark Region Committees on Biomedical Research Ethics, Denmark (M-20080063). Thirteen patients and all healthy participants gave written informed consent. For six patients informed written consent was obtained from the patients appointed 'consultee' as defined by the Mental Capacity Act (2005); in all cases this was the patient's legal guardian and the family doctor.

Clinical assessment

To assess the severity of brain injury we recorded the lowest Glasgow Coma Scale (GCS) [27] from the patients' acute medical charts. Within the first week after admission to the rehabilitation centre the experienced interdisciplinary team (physiotherapist, occupational therapist, and neuropsychologist) performed clinical assessment of patients with Rancho Los Amigos Level Cognitive Function Scale (RLAS) [28], and Functional Independence Measure (FIM) [29].

Somatosensory evoked potentials

SEPs were registered from both hemispheres with "Viking-Quest" (Viasys Healthcare, USA) from the active skin electrodes attached 3 cm posterior to C3 and C4 (10−20 system) respectively for the right and left median nerve, and with the reference electrode placed at Fz. A bipolar electrical stimulator was used. Test parameters were: stimulus duration 0.2 ms; frequency 2 Hz; intensity: 150% over the motor threshold for abductor policis brevis muscle. Five hundred responses were averaged to identify the latency of the N20 peak.

Transcranial magnetic stimulation

Magnetic stimulation was performed with a Magstim 200 (The Magstim Company Ltd, U.K.) and a Magstim figure-of-eight-shaped coil with external loop diameters of 9 cm. Both hemispheres were stimulated in patients and healthy subjects, except in one patient where the study was stopped halfway because patient showed signs of fatigue and discomfort. Electromyographic (EMG) activity was recorded from contralateral first dorsal interossei (FDI) muscle with two 9 mm diameter Ag−AgCl surface electrodes in a belly tendon montage. EMG activity was registered with a "Viking Select" device (Viasys Healthcare, USA), amplified and filtered (band pass: 10 Hz−3000 Hz), and stored on a computer for off-line analyses. Initially, maximum muscle response (M_{max}) and F-waves were measured from FDI after ulnar nerve stimulation (0.2 ms square-wave constant current pulses) at the wrist. M-wave amplitude was measured peak-to-peak. F-wave persistence was defined as number of potentials with amplitude of at least 20 μV out of 20 recordings [30]. For TMS experiments subjects wore a close-fitting cap with a 1-cm grid to ensure constant coil position during the entire session. The coil was always held tangentially to the head with the handle pointing backwards and 45° laterally from the midline [31]. The coil was placed at the cranial site from which a maximum FDI response was obtained (hotspot). The RMT, expressed as a percentage of the maximum stimulator output, was defined as the intensity needed to produce a response of 50 μV (peak-to-peak) or more in at least five of ten consecutive stimuli in the relaxed muscle [32]. Paired-pulse stimulation to measure SICI and ICF was performed according to previously published protocol [33]. The conditioning magnetic stimulus was 80% of the RMT, and the test stimulus had an intensity resulting in an unconditioned MEP (uMEP) of ∼ 1 mV. Interstimuli intervals (ISI) were 2, 3, 10, and 15 ms. Each TMS block consisted of 25 pseudorandomised stimuli: 5 single magnetic stimuli and 5 stimuli at each ISI; the interval between each stimulus was 8 s. MEP amplitudes at different ISI's were calculated as a percentage of the mean amplitude of the test pulse alone. SAI was measured in the relaxed muscle by paired-pulse stimulation paradigm [23]. Conditioning stimuli were 0.2 ms single pulses of electrical stimulation applied through

Table 1
Demographic and clinical patient characteristics.

Patient number	Age (years)	Gender	Brain injury cause	Time since insult (days)	GCS (minimum total score)	RLAS (maximum total score)	FIM (maximum total score)	Motor function, hand	Neuroimaging (CT or MRI)
1	63	M	Cardiac arrest	107	NA	8	54	Moderate paresis bilaterally	Normal
2	51	M	SAH	71	9	7	117	No motor deficit	Severe basal SAH (ACA and AP; clips, craniotomy), ventricular enlargement, VP-shunt
3	41	F	Cardiac arrest	125	NA	6	48	Moderate paresis bilaterally, myoclonus	Normal
4	49	M	TBI	152	11	8	115	No motor deficit	Multiple small haemorrhages frontal area bilaterally
5	34	M	SAH	212	3	7	118	No motor deficit	Severe SAH (ACA; clips and coil; R craniotomi), oedema R frontal, ventricular enlargement, no VP-shunt.
6	20	M	TBI	144	10	8	122	No motor deficit	Traumatic SAH, multiple subcortical haemorrhages fronto-parietal ilaterally
7	59	F	SAH	119	3	6	107	No motor deficit	Central SAH (AB; coil)
8	49	M	TBI	125	3	6	23	Right severe paresis, left moderate paresis	Ischemic lesions L cerebellum, L pons and L medulla oblongata
9	39	M	TBI	100	10	6	120	No motor deficit	Severe contusions with oedema L temporal and frontal, R temporal
10	54	F	SAH	73	4	3	20	Severe paresis bilaterally	Severe SAH (AB; coil), ventricular enlargement, L VP-shunt
11	65	F	SAH	120	6	3	18	Severe paresis bilaterally	Severe SAH (ACA; clips), infarcts parietal bilaterally, ventricular enlargement, R VP-shunt
12	49	F	Cardiac arrest	51	NA	7	86	No paresis, myoclonus	Normal
13	47	F	SAH	103	5	5	32	Moderate paresis bilaterally	Severe SAH (ACA; clips), infarcts parasagital frontal bilaterally
14	63	F	SAH	64	3	7	93	Moderate paresis bilaterally	Severe SAH (AB; coil, external drainage), ventricular enlargement, no VP-shunt
15	56	F	SAH	86	11	6	92	No motor deficit	Severe SAH (AP; clips), infarcts parasagitalt R frontal
16	66	F	SAH	342	4	4	21	Severe paresis bilaterally	SAH, infarcts L temporal and occipital; L cerebral peduncle, cerebellum, iskaemic lesions frontal and parietal bilaterally, ventricular enlargement, no VP-shunt.
17	62	F	SAH	36	3	3	18	Severe paresis bilaterally	Severe SAH (ACA; clips), infarcts frontal bilaterally, R occipital, iskaemic lesions periventricular deep white matter
18	48	F	Hypophysis adenoma/ postoperative infection	243	4	2	18	Severe paresis bilaterally	Ventricular enlargement, hygroma R frontal, L VP-shunt
19	25	M	TBI	249	3	8	NA	No motor deficit	Diffuse axonal injury, haemorrhage R frontotemporal, L thalamus and mesencephalon

TBI, traumatic brain injury; SAH, subarachnoidal haemorrhage; GCS, Glasgow Coma Scale: three sub-scales: motor, verbal, arousal functions (minimum score 3, maximum 15); RLAS, Ranchos Los Amigos Levels of Cognitive Functioning Assessment Scale: 1= no response, 2 = generalized response, 3 = localized response, 4 = confused, agitated response, 5 = confused, inappropriate, nonagitated response, 6 = confused, appropriate response, 7 = automatic, appropriate response, 8 = purposeful, appropriate response; FIM, Functional Independence Measure : 18 items are grouped into seven sub-scales: self-care, sphincter control, mobility, locomotion, communication, psychological adjustment, and cognitive functions (minimum score 18, maximum 126); NA, not assessed; ACA, anterior communicating artery; AP, posterior artery; AB, basilar artery; VP, ventriculo-peritoneal shunt; R, right; L, left.

Table 2
Electrophysiological and single-pulse TMS measures.

Test, mean ± SD	Healthy, dominant hand	Healthy, non-dominant hand	Patients, dominant hand	Patients, non-dominant hand
M_{max} (mV)	13.5 ± 4.3	14.0 ± 3.1	10.5 ± 5.8	9.5 ± 5.7
F-wave persistence (number)	18 ± 5	19 ± 6	19 ± 4	19 ± 1
MEP latency (ms)	23.0 ± 1.4	23.6 ± 1.8	23.6 ± 1.7	22.6 ± 1.4
PMCT (ms)	16.3 ± 1.2	16.2 ± 1.2	16.04 ± 1.5	16.03 ± 1.4
CMCT (ms)	7.3 ± 1.2	6.8 ± 1.4	7.4 ± 1.3	6.7 ± 0.9
RMT (% MSO)	47.8 ± 7.6	52.2 ± 13	45.6 ± 6.8	47.1 ± 12.7
uMEP (mV)	1.4 ± 1.2	1.4 ± 1.4	1.2 ± 1.1	1.3 ± 0.5

Values are mean ± standard deviation. Abbreviations: M max, maximum muscle response; F-wave persistence, number of potentials with amplitude of at least 20 μV out of 20 F-wave recordings; PMCT, peripheral motor conduction time; CMCT, central motor conduction time; SEP, sensory evoked potential; MEP, motor evoked potential; RMT, resting motor threshold; MSO, maximal stimulator output; uMEP, unconditioned MEP to the single magnetic test stimulus.

bipolar electrodes to the median nerve at the wrist with the cathode positioned proximally. The intensity of the stimuli was set at 150% over the motor threshold for abductor policis brevis muscle [23], and the magnetic test stimulus had an intensity resulting in uMEP of ∼1 mV. ISI's were determined relatively to the latency of the N20 component of the SEP: N20 − 2 ms, N20 + 0 ms, N20 + 2 ms, N20 + 4 ms, N20 + 6 ms, N20 + 8 ms, N20 + 15 ms. Each TMS block consisted of 40 pseudorandomised stimuli: 5 single magnetic stimuli and 5 stimuli at each ISI; the interval between each stimulus was 8 s.

Statistical analysis

The analyses were performed using the statistical package STATA (Stata version 9.2, Texas, U.S.A.). All electrophysiological parameters were analysed separately; comparison between the parameters obtained from different hemispheres was performed using a Wilcoxon matched-pairs signed-ranks tests; parameters of patient group were compared with those of the controls by means of Mann−Whitney tests. Comparisons between the time courses of the conditioning effect (magnetic stimulation in the paired-pulse SICI and ICF protocol and electrical stimulation at the wrist in the SAI protocol) at different ISI's in different groups (patients and controls) were made using a two factor repeated measures analysis of variance (ANOVA) with ISI and group as the main factors (and the interaction between them). A statistical difference in the ANOVAs was followed by post hoc two-sample t-tests on mean data from patients and controls. Data in the 2 and 3 ms ISI and 10 and 15 ms ISI were pooled for statistical analysis [34]. MEP data were logarithm transformed in order to achieve normal distribution. The relationship between clinical scores and electrophysiological parameters were evaluated using a Spearman's correlation coefficient. Statistical significance levels were set to $P = 0.05$.

Results

Basic electrophysiological measures

Basic electrophysiological measures (M_{max}, F-wave persistence, PMCT, CMCT, SEP, and MEP latencies) and TMS parameters (RMT, SICI, ICF, and SAI) were not different between the dominant and non-dominant hemisphere in patients or controls ($P > 0.05$, Table 2). Therefore further statistical analyses between patient and control groups were performed on parameters obtained from the dominant hemisphere.

SICI and ICF

Examples of uMEP and SICI/ICF are given in Fig. 1A and C.

Comparisons between time courses of the conditioning effect at different ISI's in patients and healthy controls revealed significant difference between these two groups ($F(3,74) = 6.55$, $P = 0.0005$). SICI was reduced in patients compared to healthy controls

(73.4% ± 43.7% in patients compared to 33.4% ± 22.2 % of the test response in healthy controls, $P = 0.02$). No difference was observed in the ICF parameters ($P > 0.05$), see Fig. 2. GCS was correlated to the amount of SICI (Spearman's rho = −0.59, $P = 0.0181$). No correlation was found between SICI and RLAS (Spearman's rho = −0.17, $P = 0.5$) or FIM (Spearman's rho = −0.44, $P = 0.065$), see Fig. 3.

SAI

Comparisons between time courses of the conditioning effect at different ISI in patients and healthy controls revealed significant difference between these two groups ($F(6,156) = 2.82$, $P = 0.012$). The responses were inhibited in healthy controls with the most pronounced inhibition when the median nerve stimulus was given at N20 + 2 ms before the TMS stimulus ($P = 0.004$). At this ISI interval the amount of inhibition was 84.5 ± 40.6% of the test size in patients and 49.5 ± 27.2% of the test size in controls, with a significant difference between the groups ($P = 0.027$), see Fig. 4. Examples of uMEP and SAI at N20 + 2 ms are given in Fig. 1B and D.

We found no correlation between SAI and clinical scores (Spearman's rho = 0.02, $P = 0.93$ for GCS; 0.16, $P = 0.54$ for FIM; −0.07, $P = 0.76$ for RLAS).

Discussion

The current study evaluated several excitatory and inhibitory phenomena in patients with anoxic, traumatic, and non-traumatic diffuse brain injury, and showed that, SICI and SAI showed significant differences between patients and healthy controls (while the RMT and ICF was not altered). In addition, the findings revealed a relationship between SICI and the severity of brain injury.

The relationship between changes in SICI/ICF and motor cortex plasticity has been investigated in the human motor cortex in different conditions. Our results are in agreement with several paired TMS studies reporting a significant decrease in SICI in the affected hemisphere in stroke patients in the acute phase and in the early stages of recovery [10,11,35,36]. Additionally, Di Lazzaro et al. [37] demonstrated that through theta burst stimulation there was a reduction in the MT, an increase in the MEP amplitude, and a reduction in SICI in the affected hemisphere of stroke patients. On the contrary, no changes were found in SICI in patients with diffuse TBI two years after the injury [12]. The discrepancy in the results between the current study and previous studies could be explained by the aetiology of the brain injury and the shorter period after the insult in our study population. The lesion-induced suppression of inhibition develops as fast as one day after the lesion induction [7,9], reaches a peak in the first week post lesion, and slowly and only partially recovers to a subnormal level two months after the lesion induction [6]. The acute contralesional disinhibition also seems to normalize over time [10,11].

In the current study, a significant relationship was found between SICI and the severity of brain injury. Our findings confirm the results
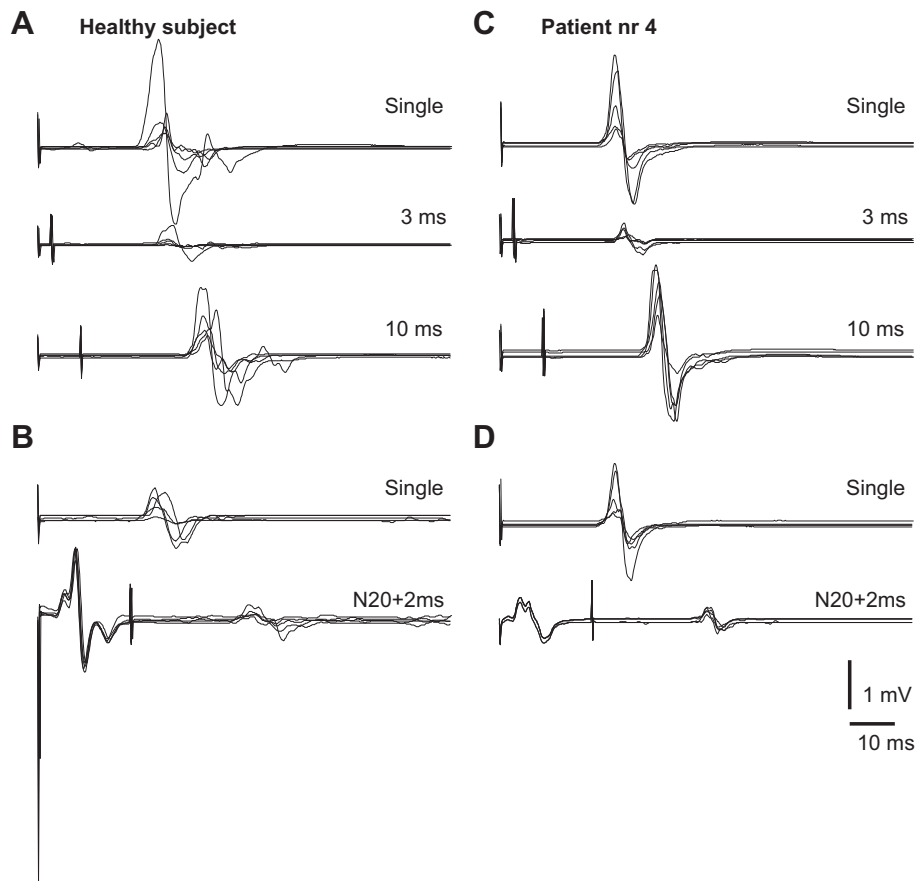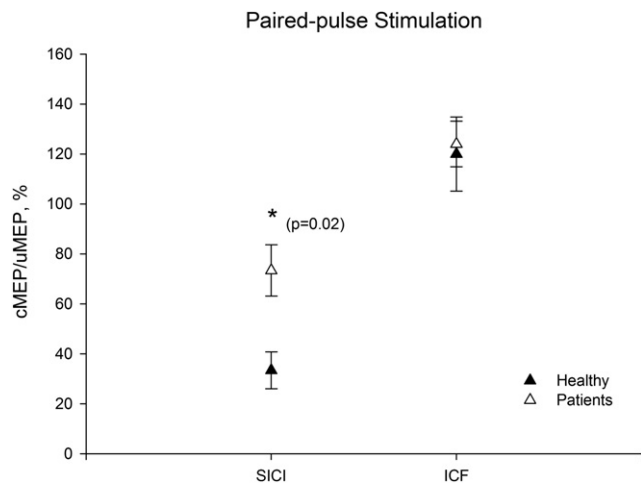
Figure 1. Examples of Motor Evoked Potentials (MEPs). An unconditioned and a conditioned Interstimuli intervals, (ISI = 3 ms, ISI = 10 ms, and ISI = N20 + 2 ms) MEP is shown from a healthy control (A and B) and a patient (C and D).

of Takeuchi et al. [15] showing a strong correlation of GCS with the cortical inhibition in patients with TBI. However, we observed no statistically significant correlations between SICI and SAI parameters and the cognitive and functional level of the patient assessed using the RLAS and FIM. Also, Di Lazzaro et al. [37] showed that an increase in MEP amplitude significantly correlated with recovery at 6 months following stroke, while the amount of SICI did not predict long-term recovery. However, it was shown that behavioural gains in motor function induced by somatosensory stimulation of the paretic hand were accompanied by a reduction in SICI and ICF in the ipsilesional primary motor area in patients with chronic stroke [38]. Due to the small sample size in the current study, the possible explanation for the lack of correlation between neurophysiological measures and clinical scores could be that the respective scores (i.e. RLAS and FIM) are not sensitive enough to characterize the diversity and the multiplicity of physical and cognitive impairments in each individual patient. Therefore, the changes in intracortical inhibition and correlation with function at any particular time point may be highly dependent on the initial patient characteristics [10,11,39]. For example, in the current study, patient no.7 with the severe brain injury due to subarachnoidal haemorrhage (GCS of 3 point in the acute period), showed pronounced SICI and remarkable functional improvement approximately 4 months after injury (FIM of 107 points at the discharge). Further studies with more homogeneous populations and more detailed and complex physical and neuro-psychological examinations would provide more information about the clinical correlates and relevance of the excitability changes in patients with brain injury.

Pharmacological studies have confirmed that SICI depends on GABA receptor activity [22,40]. Several studies indicate that cortical injuries, independent of their aetiology, can also lead to a reduced strength of GABA-mediated inhibitory transmission [6–9]. The reduced inhibition seems to be a general phenomenon taking place as a consequence of widespread neuronal death [41]. The loss of inhibition in the affected hemisphere could be a compensatory mechanism, which may represent an adaptive form of plasticity in the motor cortex [10,35,42,43], facilitating motor recovery [36]. Additionally, functional recovery is likely to be related to changes in distributed neuronal networks rather than in individual cortical regions [44,45]. Interhemispheric inhibition is likely altered after stroke [46]. Therefore, in future studies local changes in excitability in motor areas and assessment of interhemispheric inhibitory phenomena should be assessed. The present study showed also a significantly decreased SAI in brain injury patients compared to healthy controls. Our findings are in line with the results of Fujiki et al. [12] demonstrating decreased SAI in patients with diffuse TBI. Hypothesis of the impaired cholinergic neuronal function in brain injury is also supported by the preliminary evidence that donepezil improves memory during post acute brain injury rehabilitation [47,48]. The mechanisms behind reduced SAI in brain injury is unclear, but could involve either direct inhibition of motor cortex from fast conducting afferents, or withdrawal of tonic facilitation from other structures, such as thalamus [49]. Another possibility is that the subcortical lesions interrupt ascending cholinergic axons determining cortical cholinergic denervation as it was previously suggested for patients with multi-infarcts [50]. Cholinergic axons
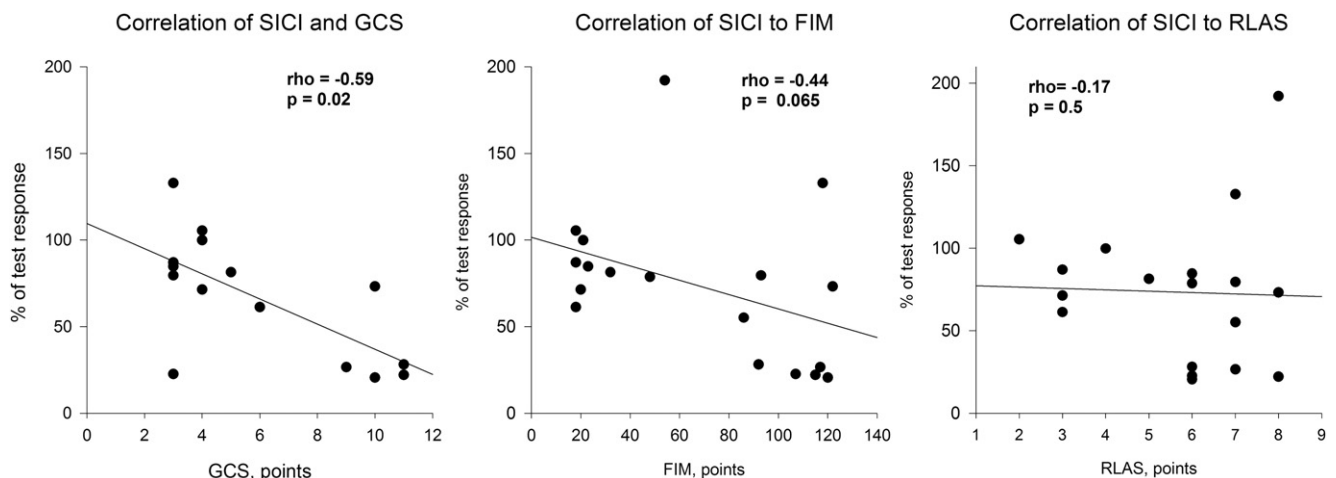
Figure 4. Short latency afferent inhibition by somatosensory input from the median nerve in patient (black triangles) and control group (open triangles). Ratios of mean conditioned/unconditioned MEP amplitude are plotted. Conditioning median nerve stimulation preceded TMS of the contralateral motor cortex by seven different ISIs, which were corrected for the latency of the N20 component of the somatosensory evoked potential in each subject. The data presented are mean values ± SEM. Comparisons between time courses of the conditioning median nerve stimulation revealed significant difference between patient and control groups (two factor ANOVA with ISI ($F = 9.88$, $P = 0.0000$) and group ($F = 0.53$, $P = 0.47$) as the main factors and the interaction between them ($F = 2.18$, $P = 0.047$). *Post hoc* analysis showed the most prominent difference between the groups when the median nerve stimulus was given at N20 + 2 ms before the cortical stimulus ($P = 0.027$, two-sample *t*-test). Abbreviations: MEP, motor evoked potential; ISI, interstimuli intervals.

Limitations of the study

It is important to highlight that the TMS measurements in the current study could be influenced by the centrally acting drugs administered to the patients (as standard care in the rehabilitation hospital). It has been shown that benzodiazepines can reduce ICF and SAI, and increase SICI [57], however, the influence of other centrally acting drugs on cortical excitability has not been thoroughly investigated. While some information has been gathered on how individual drugs influence TMS [65], the effects of different drug combinations, often used in severely brain damaged patients, remains unclear. Further studies without any central nervous system modulating medication would improve the understanding of the underlying pathophysiological mechanisms in brain injury. A second caveat relates to the presence of hydrocephalus, which might affect both functional status and TMS measurements. In the current study, seven patients had a ventricular enlargement confirmed with a CT or MRI examination and three of patients were treated with ventriculo-peritoneal shunt. The patients had a diverse functional outcome with FIM scores varying from 18 to 118. The effect of hydrocephalus and shunting on TMS parameters has not been thoroughly investigated. However, the study performed in patients with symptomatic hydrocephalus of different origin, showed MEP amplitudes and corticospinal conduction times within the normal range [66]. In the current study, we had only limited information on cerebrospinal fluid pressure at the time of the TMS investigation. However, none of the patients studied had the clinical signs of the elevated cerebrospinal fluid pressure. In future studies, confirmation of diffuse cerebral atrophy and secondary ventricular enlargement or presence of hydrocephalus with elevation of cerebrospinal fluid pressure is required. Finally, in the current study here was heterogeneity in the size, location, severity, and type of focal lesions in the participants with different brain injury aetiology. Future studies should correlate the amount of inhibition as measured by TMS with the abnormal brain anatomy in the corpus callosum, internal capsule, cerebral peduncle, and thalamus as measured using MRI (e.g. diffusion tensor imaging, fractional anisotropy, voxel-based morphometry). Nevertheless, this study provides detailed information on the integrity of the corticospinal sensorimotor pathways in patients with anoxic, traumatic, and non-traumatic diffuse brain injury.

In conclusion, the current study showed significantly reduced SICI and SAI in patients with anoxic, traumatic, and non-traumatic diffuse brain injury. Moreover, the significant correlation was found between the amount of intracortical inhibition and the severity of brain injury. Reduced cortical inhibition might suggest an impairment of the GABAergic and cholinergic systems in the primary sensorimotor cortex. Pharmacological studies with homogeneous brain injury populations would allow further assessment of this hypothesis, which, if confirmed, might offer prognostic surrogate markers and suggest novel therapeutic strategies.

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