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ORIGINAL COMMUNICATION

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Functional involvement of cerebral cortex in adult sleepwalking

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Abstract The pathophysiology of adult sleepwalking is still poorly understood. However, it is widely accepted that sleepwalking is a disorder of arousal. Arousal circuits widely project to the cortex, including motor cortex. We hypothesized that functional abnormality of these circuits could lead to changes in cortical excitability in sleepwalkers, even during wakefulness. We used transcranial magnetic stimulation (TMS) to examine the excitability of the human motor cortex during wakefulness in a group of adult sleepwalkers. When compared with the healthy control group, short interval intracortical inhibition (SICI), cortical silent period (CSP) duration, and short latency afferent inhibition (SAI) were reduced in adult sleepwalkers during wakefulness. Mean CSP duration was shorter in patients than in controls (80.9 ± 41 ms vs. 139.4 ± 37 ms; p = 0.0040). Mean SICI was significantly reduced in patients than in controls (73.5 ± 38.4% vs. 36.7 ± 13.1%; p = 0.0061). Mean SAI was also significantly reduced in patients than in controls (65.8 ± 14.2% vs. 42.8 ± 16.9%; p = 0.0053). This neurophysiological study suggests that there are alterations in sleepwalkers consistent with an impaired efficiency of inhibitory circuits during wakefulness. This inhibitory impairment could represent the neurophysiological correlate of brain "abnormalities" of sleepwalkers like "immaturity" of some neural circuits, synapses, or receptors.

Key words transcranial magnetic stimulation · adult sleepwalking · GABA · sleep

Introduction

Sleepwalking is considered to be a disorder of arousal, characterized by complex behavior during slow-wave sleep and which results in walking during sleep. Episodes can range from simply sitting up in bed to walking and even to frantic apparent attempts to "escape." Patients may be difficult to awake, but when awoken, they are often confused and amnesic of the episode's events [1].

Since it is widely accepted that sleepwalking is a disorder of arousal [2], its anatomical substrates presumably lie in the deep brain, and particularly in those structures involved in control of the arousal mechanisms [3]. Confirming this anatomical substrate, activation of thalamocingulate pathways and persistent deactivation of other thalamocortical

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Table 1 Demographic and sleep characteristics of sleepwalkers

Patients	Sex	Age	Age of onset	Associated parasomnias	Family history of SW	Estimated frequency	Severity	Treatment
1	F	21	4		Yes	3–4/week	Severe	Clonazepam 10 mg[a]
2	M	38	4	Bruxism	No	1/week	Moderate	No
3	M	26	5	Sleepterror	Yes	4–5/week	Severe	Clonazepam 10 mg[a]
4	F	29	4		Yes	2–3/week	Severe	No
5	F	24	5	Sleepterror	No	3/week	Severe (pi)	Clonazepam 5 mg[b]
6	M	49	8	Sleepterror	Yes	2/week	Severe	No
7	M	24	6		Yes	1–2/week	Moderate	No
8	M	42	12		No	2/week	Severe	No

SW = Sleepwalking
pi = frequent physical injury
[a]Treatment started after the neurophysiological examination
[b]Withdrawn because of excessive daytime sleepiness

arousal systems – during a sleepwalking episode – have been reported [4].

Sleepwalking is more common in childhood, yet may persist into adulthood; so it is conceivable that an abnormal maturation of one or some of these neural circuits could be responsible for sleepwalking. We therefore hypothesized that functional abnormality of these circuits could lead to changes in cortical excitability in sleepwalkers, even during wakefulness.

Therefore, non-invasive methods of assessment of in vivo brain activity – during wakefulness – could be advantageous in the understanding of the pathophysiology of the disease. Transcranial magnetic stimulation (TMS) is a non-invasive method of assessment that can be used to study the excitability of the human cortex [5]. It is well known that arousal circuits widely project to the cortex, including motor cortex [3]. We decided to study the excitability of the motor cortex for two reasons: firstly, most previous TMS studies have focused on excitability of the motor cortex, due to the relatively easy way to assess the motor output, and secondly, a number of TMS experimental protocols are now well described, even from a pharmacological point of view [5]. Another reason to study motor cortex excitability is that most of the pathological activities of sleepwalkers seem to involve motor systems (walking, movement of arms, speech, etc.). The aim of this study was to attempt to find an answer to an important question: is the sleepwalker's brain "normal" during wakefulness?

In order to answer this question, we evaluated motor cortex excitability in eight adult sleepwalkers during wakefulness.

Methods

Patients

We examined eight patients with a diagnosis of sleepwalking according to the International Classification of Sleep Disorders (2005) [1]. The main clinical and demographic characteristics of the patients are reported in Table 1. The mean age of the patients was 31.6 ± 10 years. None of the patients had taken any medication in the 60 days prior to participation in the electrophysiological study, which was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of the Medical Faculty of the Catholic University in Rome. Patients gave their informed consent before participation. After the neurophysiological study three of the patients (#1, #3, and #5) started pharmacological therapy with clonazepam. Treatment induced a subjective partial benefit in patient #3, consisting of a reported decrease in both the frequency and the duration of sleepwalking episodes and the complexity of motor behavior. Clonazepam proved completely ineffective in patient #1, and treatment was therefore withdrawn. Patient #5 reported a partial benefit from Clonazepam (reduction in the duration and motor complexity of the episodes as observed by her relatives), but she complained of severe daytime sleepiness induced by the drug. Clonazepam was therefore withdrawn. Patient #8 had been previously treated with Clonazepam. However, treatment was withdrawn as it was found to be totally ineffective.

Sleep examination

Patients and controls underwent a full-night laboratory nocturnal video-polysomnography (PSG) following adaptation. The control group consisted of 18 healthy volunteers (nine females and nine males), with a mean age of 34.4 ± 8.8 years.

Patients and controls were accompanied to the sleep laboratory at about 9:00 pm, and were discharged at 7:30 am the following morning. Sleep registration lasted from 10:30 pm to 6:30 am. Sleep was recorded by a Micromed System '98 digital polygraph (Micromed SL, Italy). A trained technician was present to collect data, and digital video monitoring was carried out throughout the PSG recording.

Recording included EEG gold leads filled with electrolyte, applied to the following locations: Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, O1, and O2; reference electrodes applied to the left (A1) and right (A2) mastoids; two electrooculographic (EOG) electrodes applied to the cantus of each eye, surface EMG of submental, intercostal muscles and tibialis anterior, airflow measured by oronasal thermocouple, thoracic and abdominal effort, EKG (V2 modified derivation).

Useful EEG recordings were available in all the cases studied.

Cortical excitability evaluation

Patients and controls underwent a study of cortical excitability (motor cortex) using TMS. The control group consisted of 12 healthy volunteers (six females and six males), with a mean age of

29.5 ± 8 years. Both patients and control subjects were studied at the same time of the day (between 10.30 am and 1.00 pm). We evaluated the following TMS parameters: (1) resting and active motor threshold (RMT and AMT), which reflect the intrinsic and extrinsically modulated excitability properties of corticospinal neurons [5, 6], (2) central motor conduction time (CMCT), which reflects the integrity of the corticospinal tract [7], (3) intracortical facilitation (ICF) to paired pulse TMS that is thought to depend upon the activity of intracortical excitatory circuits and it is also modulated by GABAergic inputs [8, 9], (4) short latency afferent inhibition (SAI) which is thought to depend upon the activity of cholinergic inhibitory circuits [10]: this sensory modulation of cortical activity could also be important in arousal produced by sensory stimulation during sleep [11], (5) short latency intracortical inhibition (SICI) to paired pulse TMS, long latency intracortical inhibition (LICI) to paired pulse TMS, and the cortical silent period (CSP), which are all believed to reflect the excitability of inhibitory GABAergic cortical circuits [6, 12, 13]. In addition, SICI reflects the activity of GABAergic inhibitory circuits mediated by GABAA receptors [6, 12]. However, LICI reflects the activity of GABAergic inhibitory circuits mediated by GABAB receptors[6, 13, 14]. The mechanisms generating CSP are – at least in part – different from those responsible for SICI, in which CSP appears to be more related to GABAB mechanisms [14]. However, the administration of lorazepam – a benzodiazepine which determines an increase of chloride channel opening frequency through the activation of GABAA receptors – induces a lengthening of CSP duration in normal subjects [6]. It is therefore conceivable that, at least in part, silent period also depends on GABAA activity, and the CSP could be considered a mixed effect of activation of both GABAA and GABAB receptors.

Magnetic stimulation was performed with a high power Magstim 200 (Magstim Co., Whitland, Dyfed, UK). A figure-of-eight coil with external loop diameters of 9 cm was held over the right motor cortex at the optimum scalp position to elicit motor responses in the contralateral first dorsal interosseous muscle (FDI). The induced current flowed in a postero-anterior direction. Both single and paired stimulation of the motor cortex were performed with the stimulator(s) connected to the Bistim Module. This reduces the maximum output of the magnetic stimulator by about 30%.

RMT was defined as the minimum stimulus intensity to produce a liminal motor evoked response (about 50 μV in 50% of trials) at rest. AMT was defined as the minimum stimulus intensity required to produce a liminal motor evoked response (about 200 μV in 50% of trials) during isometric contraction of the tested muscle at about 20% maximum [7]. CMCT was calculated by subtracting the peripheral conduction time from cervical roots to muscles (obtained by magnetic stimulation at cervical level) from the latency of responses evoked by cortical stimulation [7]. CSP was elicited whilst subjects held a tonic voluntary contraction of approximately 50% of maximal voluntary contraction (MVC). Five stimuli at 150% AMT were given. The duration of the silent period was measured from the end of the motor potential to the resumption (at any level) of sustained EMG activity. SICI and ICF were studied using the technique of Kujirai et al. [8]. Two magnetic stimuli were given through the same stimulating coil, using a Bistim module, over the motor cortex. 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 threshold. The second stimulus intensity (test) was adjusted to evoke a MEP 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) of 2, 3 and 10 ms were investigated. Five stimuli were delivered at each ISI. The subject was given audio–visual feedback at high gain to help maintain a state of complete relaxation. The amplitude of the conditioned MEPs was expressed as a percentage of the amplitude of the test MEPs. Inhibition of the conditioned responses at the two different ISIs studied was averaged to give grand mean values. Mean facilitation of the conditioned responses at 10 ms ISI was obtained.

LICI was studied as follows: Two magnetic stimuli were given through the same stimulating coil, using a Bistim module. Both conditioning and test stimuli were set at an intensity of 110% RMT. ISIs of 100 and 150 ms were investigated. Inhibition of the conditioned responses at the two different ISIs studied was averaged to give grand mean values.

Short latency afferent inhibition (SAI) was studied using the technique that has recently been described [10]. Conditioning stimuli were single pulses of electrical stimulation applied through bipolar electrodes to the left median nerve at the wrist. The intensity of the conditioning stimulus was set at just over motor threshold, to evoke a visible twitch of the thenar muscles. The intensity of the test cortical magnetic shock was adjusted to evoke a muscle response in relaxed left FDI with an amplitude of approximately 1 mV peak-to-peak. The conditioning stimulus to the peripheral nerve preceded the magnetic test stimulus. ISIs were determined relative to the latency of the N20 component of the somatosensory evoked potential evoked by stimulation of the left median nerve. The active electrode for recording the N20 potential was attached 3 cm posterior to C3 (10–20 system), and the reference was 3 cm posterior to C3. Five hundred responses were averaged to identify the latency of the N20 peak. ISIs from the latency of the N20 plus 2 ms through to N20 plus 8 ms (at 1 ms intervals) were investigated. Five stimuli were delivered at each ISI. The subject was given audio–visual feedback at high gain to help maintain a state of complete relaxation. The amplitude of the conditioned MEPs was expressed as a percentage of the amplitude of the test MEPs. The percentage inhibition of the conditioned responses at the seven different ISIs was averaged to obtain a grand mean.

Statistical analysis

Motor cortex excitability parameters were analyzed separately. The threshold for EMG responses (RMT and AMT), CMCT, duration of the CSP, SICI, LICI, ICF, and SAI were analyzed using an unpaired *t* test. In order to make corrections to the number of tests (eight in total), the significance level was adjusted to $p < 0.00625$. The presence of significant correlation between the severity of the disease (number of sleepwalking episodes per week) and pathological neurophysiological parameters (SICI, SAI, and CSP) was separately tested using the Pearson correlation coefficient.

Results

Sleep examination

PSG did not show any abnormal EEG finding in any of the patients. Furthermore, no patient presented sleep disordered breathing nor periodic limb movements during sleep. EEG arousals emerging from slow-wave sleep were noticed in all patients. Only in one patient (#4) a minor episode of sleepwalking was recorded, consisting of a brief arousal emerging from stage IV NREM, during which the patient sat on the bed, spoke a few words and returned to sleep. During the episode, EEG recordings showed the persistence of high voltage slow wave activity and diffused EMG artifacts. Notably, no EEG or respiratory abnormalities were detected prior to or during the reported episode.

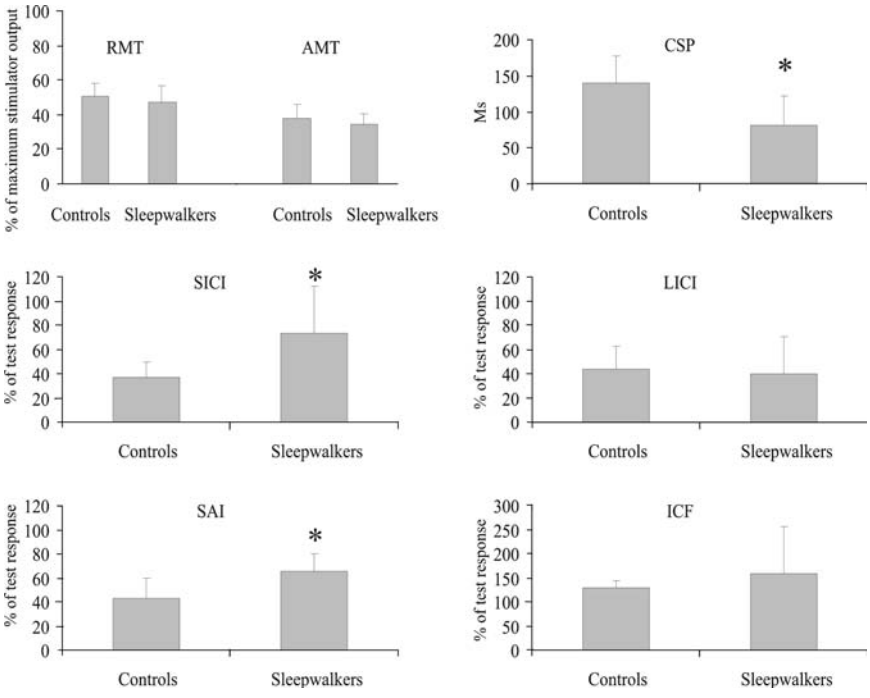

Fig. 1 Cerebral inhibitory circuits in adult sleepwalking. Short latency intracortical inhibition (SICI), long latency intracortical inhibition (LICI), short latency afferent inhibition (SAI) and cortical silent periods (CSP) in sleepwalkers and control subjects. Histograms are mean values and error bars are standard errors. Short latency intracortical inhibition, short latency afferent inhibition and cortical silent period duration were significantly reduced in sleepwalkers (*$p < 0.00625$, unpaired *t* test)

Motor cortex excitability examination

Neurophysiological results are summarized in Fig. 1.

No differences were observed between the mean RMT in sleepwalkers (47.5 ± 9.4%; $p > 0.05$) and in controls (50.6 ± 7.5%). No differences were observed between the mean AMT in patients (34.1 ± 6.2%; $p > 0.05$) and controls (38.1 ± 8.1%). Mean CSP duration was shorter in patients (80.9 ± 41 ms; $p = 0.0040$) than in controls (139.4 ± 37 ms). Mean SICI was significantly reduced in patients (73.5 ± 38.4%; $p = 0.0061$) than in controls (36.7 ± 13.1%). Mean SAI was also significantly reduced in patients (65.8 ± 14.2%; $p = 0.0053$) than in controls (42.8 ± 16.9%). LICI and ICF were similar in both groups.

No differences were observed in the CMCT between patients (5.6 ± 0.8 ms) and normal subjects (5.7 ± 0.6 ms).

Correlation analysis showed a tendency to a positive correlation between SICI and severity of the disease and a tendency to negative correlation between SAI and severity of the disease (both not statistically significant). No correlation between CSP and severity of the disease was observed (Fig. 2).

Discussion

Using TMS experiments, we found hypoexcitability of some inhibitory circuits (reduced SICI and SAI and shortened CSP) in sleepwalkers during wakefulness. This is the first report of brain abnormalities in sleepwalkers during wakefulness.

We demonstrated a functional impairment of only GABAA neurotransmission (reduced SICI and shortened CSP) with spared GABAB (normal LICI) neurotransmission within the motor cortex of sleepwalkers. SAI was also found to be reduced in sleepwalkers. This form of inhibition is thought to depend upon the activity of cholinergic inhibitory circuits [10, 15].

We can therefore hypothesize that sleepwalkers have both "less efficient" GABAA and cholinergic inhibition.

How do "less efficient" GABAA and cholinergic inhibition relate to the sleepwalking phenomena? The interpretation of the data could only be speculative and we would like to propose some possible interpretation of this reduced inhibition during wakefulness and its possible role during sleep.

GABA dysfunction and sleep

During sleep, subcortical structures have to reduce the activity of the motor cortex in order to avoid movement. Active GABAergic inhibition is a form of reduced activity of the neocortex during the sleep-wake cycle, which is more evident in REM sleep but is also present associated with disfacilitation during slow wave sleep (SWS) [16]. In addition, it has been reported that GABAA inhibition is enhanced during

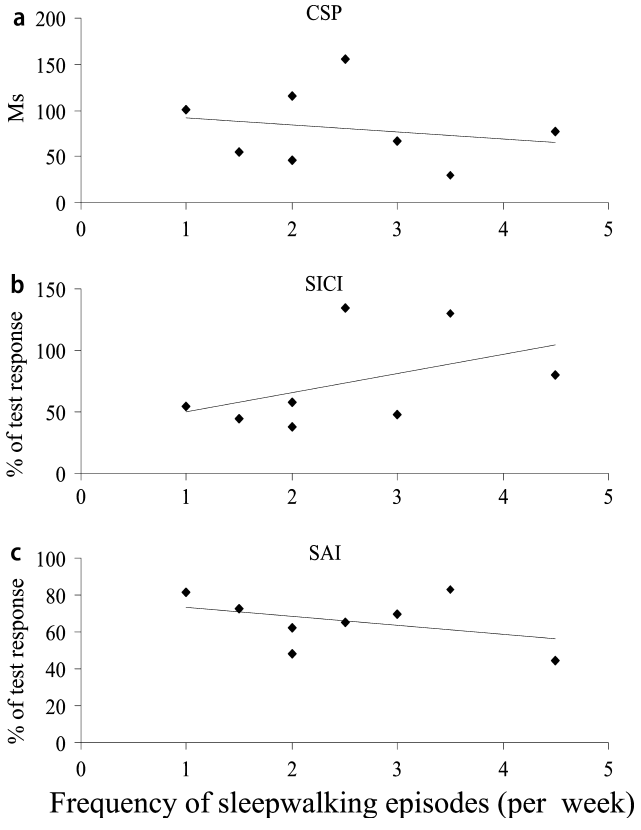

Fig. 2 Correlation analysis between CSP (A), SICI (B) and SAI (C) and severity of the disease (number of sleepwalking episodes per week). No correlation between CSP and severity of the disease was observed ($R^2 = 0.05$, $p > 0.05$, $n = 8$). Correlation analysis showed a tendency to a positive correlation between SICI and severity of the disease ($R^2 = 0.20$, $p > 0.05$, $n = 8$) and a tendency to negative correlation between SAI and severity of the disease ($R^2 = 0.15$, $p > 0.05$, $n = 8$)

SWS (stages 3 and 4) [17]. It is in these sleep stages that sleepwalkers wake up more often than control subjects. GABAA inhibition is involved in the physiological mechanism of suppression of voluntary movements [18]. For these reasons we suggest that less effective GABAergic (GABAA) inhibitory circuits, which occasionally become insufficient at stopping cortical motor activity, thus produce the sleepwalking phenomenon. We hypothesize that GABAA inhibition, during SWS (stages 3 and 4), plays an important role in avoiding movements and in preventing awakenings.

In sleepwalking, the role of subcortical structures, determining the arousal (thalamus, reticular formation, posterior hypothalamus, etc), seems critical. SICI express the function of GABAA system at cortical level, but this dysfunction could be dependent on alteration within the cortex or could be due to pathological modulation of these intracortical circuits by other parts of the brain (e.g., thalamus, basal ganglia, etc). During wakefulness, movement and motor control are normal in SW patients despite this alteration of the cortical inhibitory circuits. This is not surprising, as it is well known that a number of neurophysiological parameters are modified by pharmacological manipulation of cortical excitability with poor motor consequences [6].

Cholinergic dysfunction and sleep

Cerebral acetylcholine release is higher during wakefulness and REM sleep than during SWS [19]. Cholinergic projections facilitate the responsiveness of cortical neurons to sensory stimuli, and in this way they are involved in arousal. Sleepwalkers' difficulty in arousal during an episode could be explained by their having a weaker cholinergic activation than normally needed to change from sleep to wakefulness [1, 11].

Sleepwalkers present an inability to maintain consolidated SWS as they awake from SWS more often than control subjects. Due to reduced GABAergic inhibition of the cortex, not only nocturnal movements but also arousals should be more frequent [20]. Reduced cholinergic activity could be an associated deficiency or a "compensatory mechanism" and could explain difficulty in arousal during sleepwalking episodes. Furthermore, if reduced SAI was the only alteration in sleepwalker's brain, we would probably expect the REM stage to be critical in the pathology. Alzheimer's disease patients, for example, show a marked reduction of SAI during wakefulness [15] and sleep alterations in this pathology are mainly present in REM sleep [21]. SAI tends to correlate negatively with the severity of the disease. This means that patients with less sleepwalking episodes have more affected SAI. This data could support the hypothesis of a compensatory mechanism to avoid excessive arousal. However, due to the small number of patients reported here, this observation should be confirmed in future studies.

The "immaturity" hypothesis

Previous studies strongly suggest that the populations of inhibitory neurones involved in SICI and SAI are different [10, 15, 22]. Muscarinic blockade reduces SAI but not SICI [10]. GABAA stimulation strongly enhances SICI. The same stimulation produces different effects on SAI, depending on which benzodiazepine we use. Lorazepam markedly reduces SAI, whereas diazepam slightly increases it. This difference is probably due to the different affinity for the GABAA receptors [23]. This data suggests that the cholinergic pathway – responsible for SAI – is strongly modulated by GABAA receptors whilst SICI is strongly dependent – only – on GABAA receptors

[15, 23]. Diazepam binds non selectively all four GABAA receptor subtypes, and when this occurs, SAI increases [23]. So we can speculate that if GABAA receptor (or synapses) are "less efficient" in sleepwalkers, we can expect SICI together with SAI reduction, that is what we found.

It is well known that sleepwalking is more frequent in childhood and that it can persist into adulthood. During brain development, there are large changes in GABAA receptor binding and subunit expression. The role of GABAergic cells also seems to change during development from a neurogenic to an information-processing role [24, 25]. An immature form of GABAA receptors could be less effective in stopping movement during sleep. The strong active inhibition during REM can efficiently activate even an "immature" form of GABAA receptors and, associated with muscle atonia, movement can be prevented; but the weaker GABAergic projection, during SWS, and the presence of immature and less efficient receptors (or synapses) could be not enough to inhibit the motor cortex, so that simple or complex motor behavior and speech can be produced.

Supporting our hypothesis, anti-dopaminergic drugs and sleep deprivation, which produce decreased GABAergic intracortical inhibition [26, 27] can induce sleepwalking [28–30].

Conclusions

We suggest that concomitant dysfunction of GABA(A) and cholinergic pathways predispose the brain to sleepwalking due to the inability to maintain consolidated SWS, the inability to stop nocturnal movements, and the reduced reactivity to sensory stimuli during sleepwalking episodes.

It is interesting that similarly reduced excitability of cortical inhibition (concomitant dysfunction of GABAA and cholinergic circuits) during wakefulness has been reported in Tourette's syndrome [31]. Tourette's patients share difficulty in suppressing involuntary movements with sleepwalkers, and they have been reported to have a significantly higher prevalence of arousal disorders – in particular sleepwalking and night terrors [32]. We can therefore speculate, that this two disorders may share some common pathophysiological mechanisms.

This neurophysiological study shows that there are alterations in the excitability of some cortical GABAergic (GABAA) and cholinergic inhibitory circuits during wakefulness, and that this could represent the neurophysiological correlate of brain "abnormalities" of sleepwalkers like "immaturity" of some neural circuits, synapses or receptors.

References

1. International Classification of Sleep Disorders (2005) Diagnostic and coding manual, revised. American Academy of Sleep Medicine, Rochester, MN
2. Gaudreau H, Joncas S, Zadra A, Montplaisir J (2000) Dynamics of slow-wave activity during the NREM sleep of sleepwalkers and control subjects. Sleep 23(6):755–760
3. Jones BE (2003) Arousal systems. Front Biosci 8:s438–451
4. Bassetti C, Vella S, Donati F, Wielepp P, Weder B (2000) SPECT during sleepwalking. Lancet 356(9228):484–485
5. Hallett M (2000) Transcranial magnetic stimulation and the human brain. Nature 406:147–150
6. Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W (1996) Effects of antiepileptics drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol 40:367–378
7. Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lucking CH (1994) Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 91:79–92
8. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD (1993) Corticocortical inhibition in human motor cortex. J Physiol 471:501–519
9. Ziemann U, Chen R, Cohen LG, Hallett M (1998) Dextromethorphan decreases the excitability of the human motor cortex. Neurology 51:1320–1324
10. Di Lazzaro V, Oliviero A, Profice P, Pennisi MA, Di Giovanni S, Zito G, Tonali P, Rothwell JC (2000) Muscarinic receptor blockade has differential effects on the excitability of intracortical circuits in the human motor cortex. Exp Brain Res 135:455–461
11. Oliviero A, Molina-Leon A, Holler I, Florensa-Vila J, Siebner HR, Della Marca G, Di Lazzaro V, Teijeira-Alvarez J (2005) Reduced sensorimotor inhibition in the ipsilesional motor cortex in a patient with chronic stroke of the paramedian thalamus. Clinical Neurophysiol. 116(11):2592–2598
12. Di Lazzaro V, Oliviero A, Meglio M, Cioni B, Tamburrini G, Tonali P, Rothwell JC (2000) Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. Clin Neurophysiol 111:794–799
13. Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J (1999) Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. J Physiol 517(Pt 2):591–597
14. Sanger TD, Garg RR, Chen R (2001) Interactions between two different inhibitory systems in the human motor cortex. J Physiol 530:307–317

15. Di Lazzaro V, Oliviero A, Tonali PA, Marra C, Daniele A, Profice P, Saturno E, Pilato F, Masullo C, Rothwell JC (2002) Noninvasive in vivo assessment of cholinergic cortical circuits in AD using transcranial magnetic stimulation. Neurology 59(3):392–397
16. Timofeev I, Grenier F, Steriade M (2001) Disfacilitation and active inhibition in the neocortex during the natural sleep-wake cycle: an intracellular study. PNAS 98:1924–1929
17. Salih F, Khatami R, Steinheimer S, Hummel O, Kuhn A, Grosse P (2005) Inhibitory and excitatory intracortical circuits across the human sleep-wake cycle using paired-pulse TMS. J Physiol 565:695–701
18. Sohn YH, Wiltz K, Hallett M (2002). Effect of volitional inhibition on cortical inhibitory mechanisms. J Neurophysiol 88(1):333–338
19. Jasper HH,Tessier J (1971) Acetylcholine liberation from cerebral cortex during paradoxical (REM) sleep. Science 172(983):601–602
20. Steriade M (2004) Acetylcholine systems and rhythmic activities during the waking-sleep cycle. Prog Brain Res. 145:179–196
21. Bliwise DL (2004) Sleep disorders in Alzheimer's disease and other dementias. Clin Cornerstone 6(Suppl 1A):S16–28
22. Di Lazzaro V, Oliviero A, Saturno E, Dileone M, Pilato F, Nardone R, Ranieri F, Musumeci G, Fiorilla T, Tonali P (2005) Effects of lorazepam on short latency afferent inhibition and short latency intracortical inhibition in humans. J Physiol 564(Pt 2):661–668
23. Di Lazzaro V, Pilato F, Dileone M, Tonali PA, Ziemann U (2005) Dissociated effects of diazepam and lorazepam on short-latency afferent inhibition. J Physiol 569(Pt 1):315–323
24. Chugani DC, Muzik O, Juhasz C, Janisse JJ, Ager J, Chugani HT (2001) Postnatal maturation of human GABAA receptors measured with positron emission tomography. Ann Neurol 49(5):618–626
25. Hutcheon B, Morley P, Poulter MO (2000) Developmental change in GABAA receptor desensitization kinetics and its role in synapse function in rat cortical neurons. J Physiol 522:3–17
26. Civardi C, Boccagni C, Vicentini R, Bolamperti L, Tarletti R, Varrasi C, Monaco F, Cantello R (2001) Cortical excitability and sleep deprivation: a transcranial magnetic stimulation study. J Neurol Neurosurg Psychiatry 71(6):809–812
27. Ziemann U, Tergau F, Bruns D, Baudewig J, Paulus W (1997) Changes in human motor cortex excitability induced by dopaminergic and anti-dopaminergic drugs. Electroencephalogr Clin Neurophysiol 105(6):430–437
28. Charney DS, Kales A, Soldatos CR, Nelson JC (1979) Somnambulistic-like episodes secondary to combined lithium-neuroleptic treatment. Br J Psychiatry 135:418–424
29. Joncas S, Zadra A, Paquet J, Montplaisir J (2002) The value of sleep deprivation as a diagnostic tool in adult sleepwalkers. Neurology. 58:936–940
30. Kolivakis TT, Margolese HC, Beauclair L, Chouinard G (2001) Olanzapine-induced somnambulism. Am J Psychiatry 158:1158
31. Orth M, Amann B, Robertson MM, Rothwell JC (2005). Excitability of motor cortex inhibitory circuits in Tourette syndrome before and after single dose nicotine. Brain 128:1292–1300
32. Barabas G, Matthews WS (1985) Homogeneous clinical subgroups in children with Tourette syndrome. Pediatrics 75:73–75