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Event-related current density in primary insomnia

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Abstract. Using Low Resolution Electromagnetic Tomography (LORETA), event-related current density was investigated in 14 patients with primary insomnia and 14 controls matched for age, gender and education level. All subjects were rated on the Athens Insomnia Scale, the Hyperarousal Scale, the Hamilton Depression Rating Scale and the Beck Depression Inventory. They also completed the Selective Reminding Test and the Continuous Attention Test. Only minor elevations on depression scales were found in patients. The Continuous Attention Test did not reveal any between group differences. However, insomniacs required more trials before all the Selective Reminding Test items were learned. Insomniacs showed less event-related current density in orbitofrontal, medial prefrontal and anterior cingulate cortex, i.e. brain regions of relevance for cognition and affect. Earliest group differences appeared in the P1 time range and then were observed at the N1, N2 and P3 stages of stimulus processing. These stimulus processing differences correlated most consistently with severity of insomnia. Neuropsychological impairment correlated most strongly with less current density in Brodmann area 10.

Key words: brain functional imaging, LORETA, primary insomnia, anterior cingulate cortex, attention

INTRODUCTION

Insomnia is a common complaint. About one third of adult respondents reports some sleeping problems (Costa e Silva et al. 1996). Similar data were obtained from a representative Polish sample: trouble falling or staying asleep afflicted 24% and 29% of adults samples (Szelenberger and Skalski 1999). It should be noted that insomnia is a symptom of heterogeneous origin. Transient or short-term insomnia is related to stress experienced by normal sleepers (National Institute of Mental Health 1984), but chronic insomnia results from other disorders or falls into the distinct clinical category of primary insomnia (American Psychiatric Association 1994). The cause of primary insomnia can be attributed to psychological variables. However, several lines of evidence suggest that neurobiological alterations can also be causative. Using the Vietnam Era Twin Registry, McCarren et al. (1994) demonstrated that additive genetic effects were stronger predictors of self-reported insomnia than combat exposure. An all day increase in metabolic rate indicates that insomnia is perhaps more a disorder of hyperarousal than a disorder of sleep (Bonnet and Arand 1995). Many findings are in line with the hyperarousal hypothesis. Higher amplitudes of the P1N1 component of auditory evoked potentials (Regestein et al. 1993), as well as higher beta and lower delta activity (Lamarche and Ogilvie 1997) indicate increased cortical activation. Activation of the stress system (the hypothalamic-pituitary-adrenal axis and the sympathetic system) (Vgontzas et al. 1998) is also consistent with the hyperarousal hypothesis. Therefore, chronic insomnia is an all day disorder characterized by sleeping problems at night and worse functioning during the day. Numerous brain imaging studies have contributed insights into the neural substrate of mental disorders, but there is no systematic research aimed at identifying the neural basis of insomnia.

The objective of our study was to analyze sources of brain electrical activity during continuous attention test in patients with primary insomnia. We assumed that the same system may mediate abnormal arousal across a variety of disorders.

METHODS

Material

Data was obtained from 14 right-handed, self- or physician-referred outpatients, 6 males and 8 females (mean age: 41.2 ± 11.5, range: 21-55 years), meeting DSM-IV criteria for primary insomnia (American Psychiatric Association 1994). The insomnia had persisted for 6 months to 30 years (mean: 8.25 ± 9.66 years). Fourteen healthy right-handed volunteers recruited from the hospital staff (6 males and 8 females, mean age: 36.2 ± 11.4, range: 21-57 years), with no sleep or psychiatric disorders, pair matched for sex, age and education level, served as the control subjects. The subjects were required to be free of any prescription or nonprescription drugs for at least 2 weeks prior to the study. Possible somatic disorders were excluded by medical history, physical examination and routine blood chemistry. Benzodiazepine abuse was ruled out by urinary screening after the second night of polygraphic sleep recording. Informed consent was obtained from all participants. The study was approved by the University Ethics Committee.

Procedures

We present here data from a larger study on psychophysiological correlates of primary insomnia. The study lasted for a period of 10 days. The subjects underwent continuous 24-hour actigraphic monitoring for 7 days, psychometric assessment and whole night polysomnography for 2 nights. Psychometric assessment included the Hyperarousal Scale (HS) (Regestein et al. 1993), Beck Depression Inventory (BDI) and 17-item Hamilton Depression Rating Scale (HDRS). Severity of insomnia was measured with the 8-item version of the Athens Insomnia Scale (AIS), with a total score ranging from 0 to 24 (Soldatos 1995, Soldatos et al. 2000). Polygraphic monitoring consisted of the following parameters: EEG activity in 21 derivations, electrooculogram (EOG), submentalis electromyogram, electrocardiogram, respiratory inductance plethysmography and oxygen saturation monitoring. The absence of breathing-related sleep disorder was confirmed by visual inspection of recordings collected during the adaptation night. Sleep parameters obtained during the experimental (second) night were identified visually according to the standardized manual for sleep scoring (Rechtschaffen and Kales 1968). Using criteria of the International Classification of Sleep Disorders (American Sleep Disorders Association 1997), 9 patients were diagnosed with psychophysiological insomnia and 5 with sleep state misperception. Following two nights of sleep recording, the subjects were tested for levels of daytime

sleepiness using the Multiple Sleep Latency Test (MSLT) (Carskadon 1994). The detailed polysomnographic and MSLT results are reported elsewhere (Niemcewicz et al. 2001). Performance tests were administered the same morning as the MSLT. The performance tests included the Selective Reminding Test (SRT) (Buschke and Fuld 1974) and the Continuous Attention Test (CAT) (Tiplady 1988). The CAT items consisted of 240 random presentations of abstract shapes built up from a variable pattern of 5 dark and 4 light squares (Fig. 1). The shapes were flashed onto a computer screen for 0.1 second. The intertrial interval was randomized, varying from 1.0 to 2.5 s. The subjects were asked to press a button at the moment of detection of a direct repetition of the same pattern. The CAT items were also used as stimuli in event-related potentials (ERP) recording. The direct repetitions of the same pattern were target stimuli. The probability of target appearance was 16%. Each CAT session took approximately 8 min. The test was repeated three times in order to obtain sufficient number of ERP sweeps. Reaction time was measured and number of omissions and commissions was noted. Related to clinical symptomatology and cognitive performance, only event-related group differences are presented here at length.

ERP recording

EEG was recorded from 21 electrodes, according to the international 10-20 system, with the reference electrode placed between Fz and Cz. EOG was recorded from one channel, with electrodes fixed above and below the right eye. The sampling rate was 500 Hz, filters were set between 0.15 and 35.0 Hz. The impedance at each electrode was below 5,000 ohms.

Spatial analysis

After visual rejection of trials with artifacts, responses to correctly detected target and nontarget stimuli were averaged off-line and recalculated to the average reference. Global Field Power (GFP) and dissimilarity curves were computed (Lehmann and Scrandies 1980, Lehmann 1987) which allowed the identification of microstates corresponding to successive components. P1 latency was defined as the maximal GFP value between 60 and 126 ms, N1 - between 138 and 246 ms, N2 - between 202 and 366 ms, and P3 - between 338 and 566 ms. The sources of bioelectrical activity were computed with Low Resolution Electromagnetic Tomography (LORETA) (Pascual-Marqui et al. 1994). The present version of LORETA used the three-shell spherical head model registered to the Talairach and Tournoux human brain atlas (Talairach and Tournoux 1988, Pascual-Marqui et al. 1999, Pizzagalli et al. 2001). Computations were restricted to cortical gray matter, including hippocampi. The LORETA images represented bioelectrical power in each of the total 2,394 voxels computed with 7 mm spatial resolution.

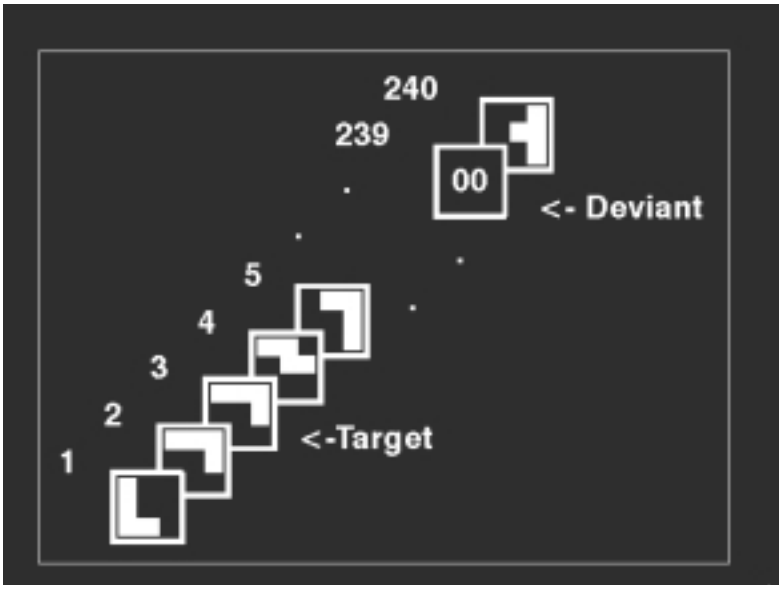

Fig. 1. Examples of Continuous Attention Test items.

Statistical evaluation

Statistical evaluation was a multistep process. In order to correct for global intersubject variance of brain electrical activity, LORETA images were first normalized by scaling all voxel values in each image to 100%. The images were then statistically compared by voxel-by-voxel independent t-tests for between groups comparison. Log-transformed values were used for statistical analysis to conform them to the normal distribution. Probability levels lower than 0.05 were considered statistically significant. Further analysis was constrained to voxels at which significant current source density differences were previously found. Non-parametric analysis (Mann-Whitney test) confirmed the significance of possible between groups differences. Correlations between LORETA images and clinical scores were computed using a rank order correlation coefficient (Spearman's rho).

RESULTS

Clinical ratings

Patients suffering from chronic insomnia scored higher on AIS, HS, BDI and HDRS (Table I). However, it should be emphasized that they did not met clinical criteria for a depressive episode as they showed only minor elevations on depression scales. All administered scales were highly correlated as is shown in the Table II.

Performance measures

Error rate was low, averaging 2.72 ± 3.30 of commissions and 5.25 ± 5.81 of omissions for controls, and 2.75 ± 4.90 of commissions and 4.25±2.90 of omissions for patients. The results did not differ significantly between the groups. Mean reaction time for correct responses was longer in patients (567.97 ± 74.01 ms) than in controls (525.70 ± 71.90 ms), but the difference was not significant. Patients required more trials before all of the SRT items were learned. Mean number of trials was 6.4 ± 2.3 for controls, and 10.0 ± 4.1 for patients (U = 34.5, P=0.028).

Table I

Clinical rating scale scores for healthy controls and insomnia patients (df=26)

	Controls	Patients	U	P
AIS	11.2 ± 1.6	20.8 ± 4.4	1.5	0.00001
HS	54.7 ± 9.7	63.3 ± 8.1	41.0	0.04
BDI	1.3 ± 2.3	6.5 ± 4.1	13.5	0.001
HDRS	0.5 ± 1.2	6.4 ± 2.2	0.0	0.00001

Table II

Correlation between results of clinical rating scales

	Spearman's rho			
	AIS	HS	BDI	HDRS
AIS		0.67*	0.81*	0.89*
HS		-	0.60*	0.48*
BDI			-	0.64*
HDRS				-

*P<0.01

Task related group differences in current density distribution

The CAT elicited activation in multiple cortical areas implicated in individual complex behaviors, perceptual, motivational and exploratory components of large-scale attentional networks (Mesulam 1990), intersecting with arousal network (Paus 2000) and emotional circuits (Lane et al. 1998). Significant group differences are presented in Table III. Insomniac patients differed from healthy sleepers in that they showed less event-related current density in orbitofrontal, medial prefrontal, anterior cingulate, premotor and parietal cortex. However, greater activation was observed in left dorsolateral prefrontal cortex. Earliest group differences appeared in the P1 component time range and could be observed across all stages of stimulus processing and in both target and non-target conditions.

Correlation between LORETA images and psychometric variables

The LORETA group differences were compared with clinical ratings using a rank order correlation coefficient. The results are presented in Table IV. Higher scoring on AIS, HS, HDRS, BDI and neuropsychological impairment (measured with SRT) was associated with less cur-

Table III

Group differences in event-related current density

Target/nontarget, ERP components Brodmann area	Stereotaxic coordinates x	y	z[1]	t_{26}
Less event-related current density in patients				
TARGET				
Component P1				
BA 7	-17	-74	50	2.12
Component N1				
BA 10	11	45	1	2.15
BA 11	11	45	-20	2.14
BA 32	11	38	8	2.15
BA 32	11	45	8	2.15
Component N2				
BA 11	4	31	-13	2.57
BA 11	-17	52	-20	2.34
Component P3				
BA 6	25	3	57	2.32
BA 6	25	3	64	2.32
BA 6	25	10	57	2.32
BA 6	-24	17	64	2.17
BA 6	-24	10	64	2.16
BA 24	4	3	43	2.78
BA 24	-3	3	43	2.78
NONTARGET				
Component P1				
BA 6	4	-11	50	2.25
BA 6	4	-18	57	2.25
BA 11	4	31	-27	2.13
BA 11	4	31	-27	2.13
Component N1				
BA 3	67	-18	36	3.38
BA 6	67	-11	29	2.38
BA 6	46	-4	57	2.14
Component P3				
BA 39	32	-67	29	2.56
Greater event-related current density in patients				
TARGET				
Component N2				
BA 19	-52	-74	-6	-2.63
BA 19	-52	-74	1	-2.63
BA 37	-59	-67	1	-2.63
Component P3				
BA 46	-52	31	22	-2.56
NONTARGET				
Component P1				
BA 2	-59	-18	22	-2.11
BA 43	-66	-18	22	-2.11
Component P3				
BA 6	-59	-4	29	-2.29
BA 6	-52	-4	29	-2.29
BA 6	-59	-4	36	-2.29
BA 40	-59	-39	29	-2.71

[1]Coordinates are in millimeters, x is the lateral distance from the midline (positive, right), y is the anteroposterior distance from the anterior commissure (positive, anterior), and z is the height relative to the anterior commissure-posterior commissure plane (positive, dorsal).

rent density in multiple areas of large-scale neurocognitive networks. These between groups differences correlated most consistently with severity of insomnia measured *via* AIS. Neuropsychological impairment showed strongest correlation with less current density in Brodmann area 10. Figure 2 shows brain areas where there were negative correlations between event-related current density and psychometric variables. There were also positive associations between current density and psychometric variables (Fig. 3), for example greater activation in the left dorsolateral prefrontal cortex was related to scoring on AIS, HDRS and BDI.

DISCUSSION

As yet, brain structures contributing to abnormal arousal in insomnia and associated cognitive impairment have not been defined. To our best knowledge, there is only one study using functional neuroimaging in primary insomnia. Nofzinger et al. (2000) found correlations between beta power in NREM sleep and relative cerebral glucose metabolism in the ventromedial prefrontal cortex.

In the present study, we applied Low Resolution Electromagnetic Tomography (LORETA) (Pascual-Marqui et al. 1994), a novel non-invasive method for localizing electrical activity (i.e. current density) in the brain. Basing on multichannel surface EEG recordings, LORETA images reflect synchronized neuronal mass activity. Combined with cognitive tasks, the method allows testing neuroanatomical hypotheses and identifying brain regions involved in cognition and emotion (Pascual-Marqui et al. 1994, Anderer et al. 1998, Strik et

Table IV

Correlations between event-related current density and psychometric variables

Target/ nontarget, ERP components	x	y	z	Spearman's rho				
				AIS	HS	HDRS	BDI	SRT
Less event-related current density in patients								
TARGET								
P1 / BA 7	-17	-74	50	-0.742**	-0.384*	-0.652**	-0.569**	-0.362*
N1 / BA 10	11	45	1	-0.340*				-0.438*
BA 11	11	45	-20	-0.449				
BA 32	11	38	8					-0.392*
BA 32	11	45	8					-0.397*
N2 / BA 11	4	31	-13			-0.363*		
BA 11	-17	52	-20			-0.384*		
P3 / BA 6	25	3	57	-0.518**		-0.517**	-0.370*	
BA 6	25	3	64	-0.513**		0.457*	-0.384	
BA 6	25	10	57	-0.549**		-0.572**		
BA 6	-24	17	64	-0.471**		-0.516**		
BA 6	-24	10	64	-0.430**		-0.394*		
BA24	4	3	43	-0.639**	-0.358*	-0.550**	-0.447*	
BA24	-3	3	43	-0.637**	-0.363*	-0.554**	-0.441	
NONTARGET								
P1 / BA 6	4	-11	50	-0.377*		-0.342*	-0.564**	
BA 6	4	-18	57	-0.377*		-0.391*	-0.540**	
N1 / BA 3	67	-18	36	-0.438*		-0.346*		
BA 6	67	-11	29	-0.345*		-0.362*		
P3 / BA 39	32	-67	29	-0.389*	-0.349*		-0.425*	
Greater event-related current density in patients								
TARGET								
N2 / BA 19	-52	-74	-6	0.414*		0.399*		
BA 19	-52	-74	1	0.443*	0.343*	0.426*		
BA 37	-59	-67	1	0.431*		0.438*		
P3/ BA 46	-52	31	22	0.387*		0.415*	0.350*	
NONTARGET								
P3/ BA 6	-59	-4	29	0.375*		0.366*		0.405*
BA 6	-52	-4	29	0.357*		0.372*		0.366*
BA 6	-59	-4	36	0.368*		0.376*		0.403*

* Significant at the 0.05 level (one-tailed); ** Significant at the 0.01 level (one-tailed)

al. 1998, Pizzagalli et al. 2000, Isotani et al. 2001, Koles et al. 2001). The method has also been used to localize epileptiform activity (Lantz et al. 1997). It has been successful in indicating the brain abnormalities most likely to underlie attention-deficit disorder (Brandeis et al. 1998), major depression (Pizzagalli et al. 2001) and schizophrenia (Pascual-Marqui et al. 1999, Mulert et al. 2001). Moreover, LORETA results are highly consistent with previous functional neuroimaging studies (Mulert et al. 2001, Pizzagalli et al. 2001).

We identified a variety of localized changes in a distributed neurocognitive network that may be functionally abnormal in chronic insomnia. Focusing here only on the issue of between groups differences, we found

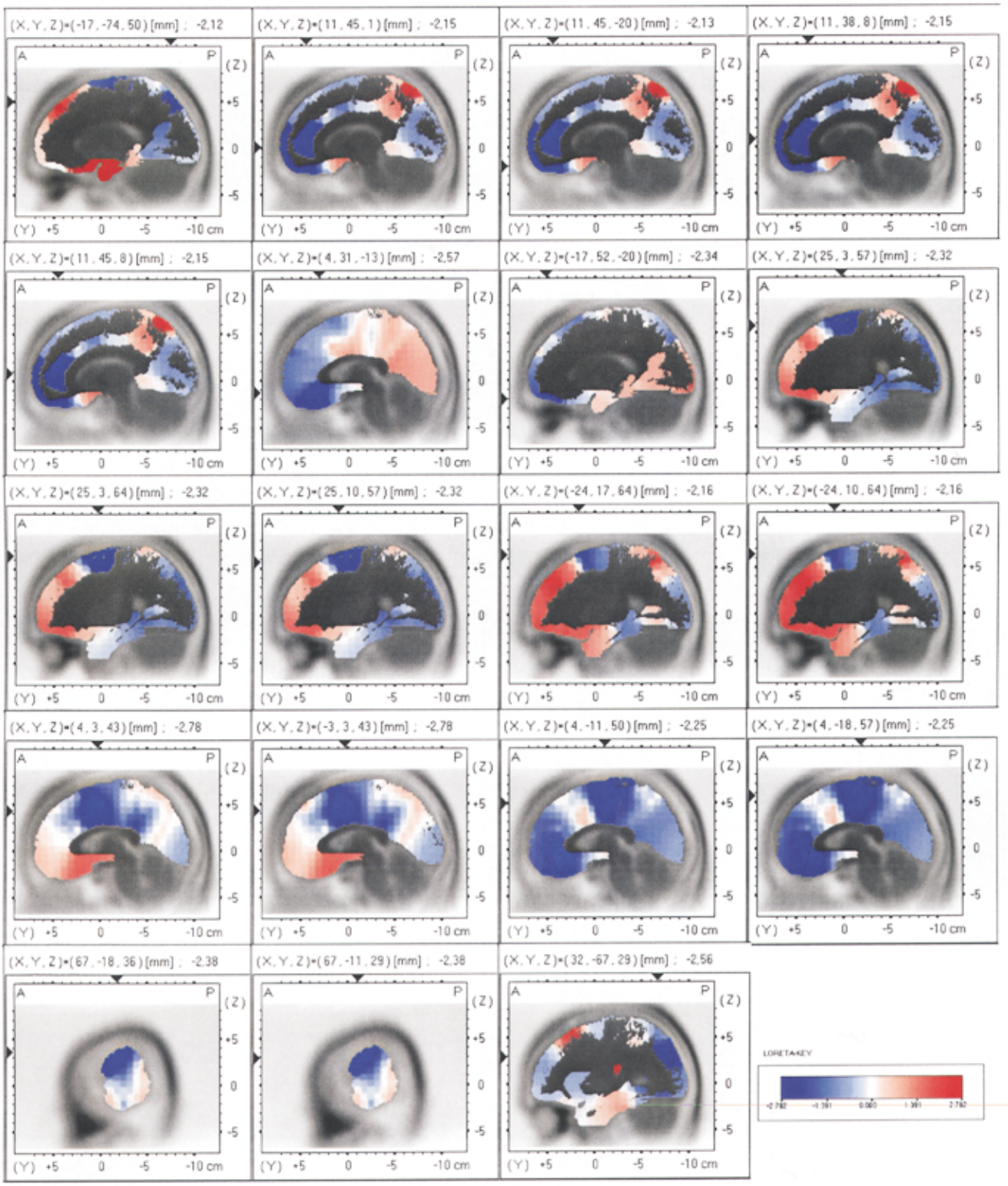

Fig. 2. Sagittal LORETA images showing areas of less event-related current density in insomniacs, as compared with control subjects. Blue colour indicates less current density in insomniacs. The black arrows indicate areas where extreme *t* values (top right of every image) were found. A, anterior, P, posterior.

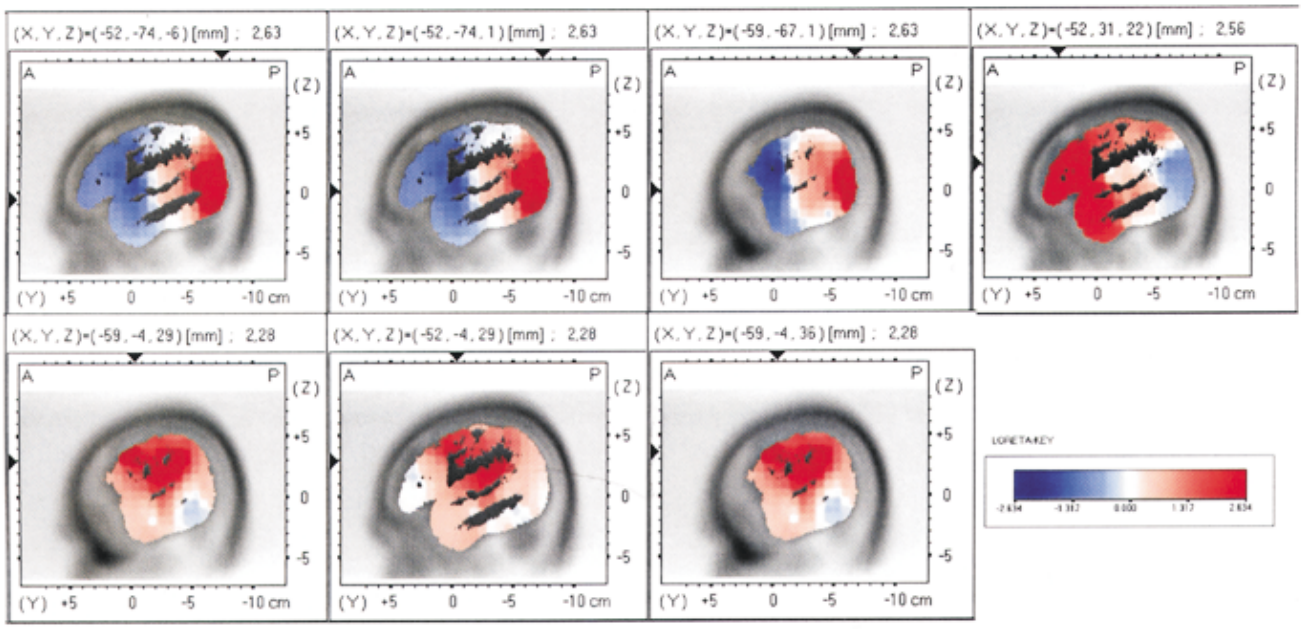

Fig. 3. Sagittal LORETA images showing areas of greater event-related current density in insomniacs, as compared with control subjects. Red colour indicates greater current density in insomniacs. The black arrows indicate areas where extreme *t* values (top right of every image) were found. A, anterior, P, posterior.

that insomniacs showed less current density in orbitofrontal, medial prefrontal and anterior cingulate cortex. These cortical sites were previously posited to regulate affect and cognitive performance (Fig. 2).

Decreases in activity were observed in the orbital gyri, and left and right area 11 according to the criteria of Frey and Petrides. These cortical regions are key areas in the processing of new information (Frey and Petrides 2000).

Less current density in the anterior cingulate is of special interest because there is evidence that cingulate cortex exerts modulatory effects on other regions (Fletcher et al. 1999). Therefore, the blunted activation in the cognitive subdivision of anterior cingulate cortex during the P3 time range can be a crucial finding. Normal subjects show activation in this area during cognitively demanding tasks (Bush et al 1998) and deactivation during induced emotions (Lane et al. 1998). Deactivation was also found in patients with depression, in resting state and during cognitive performance (Bench et al. 1992, Elliot et al. 1997). This deficit has, however, little specifity. Patients with attention-deficit disorder also do not activate the cognitive subdivision of the anterior cingulate during cognitive tasks (Bush et al. 1999). Using LORETA, Mulert et al. (2001) recently confirmed anterior cingulate suppression in schizophrenics.

We found also less current density in medial prefrontal cortex in the insomnia patients. It was already noted above that the neuropsychological impairments showed strongest correlation with less current density in Brodmann area 10. Probably this deficit also has little specifity. Associated with cognitive impairment, significant decrease in regional blood flow in the same area was reported in patients with major depressive disorder (Bench et al. 1992).

Consequently, there is a question of relationship of primary insomnia to other DSM-IV axis I mental disorders. A high prevalence of psychopathology is found in chronic insomnia. Psychiatric disorder was rated as a contributing factor for 77% of patients who received a first diagnosis of primary insomnia (Nowell et al. 1997). Although we depend here on inferences drawn from different neuroimaging modalities, we assume that the same systems may mediate abnormal arousal across a variety of functional psychiatric disorders. A considerable overlap in neurobiological deficits does not challenge clinical distinctions. We do not pinpoint the cause of insomnia. Our data indicates only functional consequences of the disorder and brain circuits that may mediate its expression.

In the present study we confirmed our previous finding of learning impairment correlated with severity of

insomnia (Szelenberger and Niemcewicz 2000). Impaired daytime functioning is a diagnostic feature of chronic insomnia. However, it has proven difficult to identify possible cognitive deficits. Many reports showed no significant performance difference between insomniacs and controls (for review see: Sateia et al. 2000). This notwithstanding, a few studies did confirm some deficits. For example, Hauri (1997) showed that insomniacs performed worse on reaction time and they forgot more numbers on the Digit Span Test. These results were uncorrelated with EEG sleep parameters. It is worth noting that our patients did not perform worse on the CAT; number of correct detections and false alarms and reaction time did not show significant between groups differences, but LORETA revealed covert processing differences between insomniacs and healthy subjects.

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