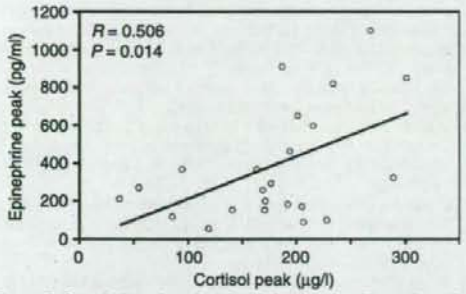

Figure 3 Correlation of peak epinephrine levels with peak cortisol levels during the insulin tolerance test in 23 patients with pituitary adenoma. To convert for epinephrine and cortisol to nanomoles per liter, multiply by 0.0005458 and 2.759 respectively.

cause of the reduction in epinephrine reserve observed in our patients with pituitary adenoma. In our study, seven patients had secondary adrenal insufficiency, three of whom had been treated with replacement of hydrocortisone. Diminished epinephrine response was observed similarly in the patients with secondary adrenal insufficiency, irrespective of hydrocortisone replacement. Thus, glucocorticoid replacement therapy is suggested not to ameliorate the epinephrine response to insulin-induced hypoglycemia. However, all patients, only seven of whom had secondary adrenal insufficiency, showed diminished epinephrine response to the hypoglycemic stimulus, so it is unlikely that secondary adrenal insufficiency *per se* is the direct cause of the reduction in epinephrine reserve. Prolactin has been shown to stimulate catecholamine synthesis in rat hypothalamic cells (28). There were no patients with prolactin deficiency in our study, suggesting that prolactin deficiency is not involved in the decreased epinephrine reserve.

When severe impairment of the epinephrine response was defined as a peak epinephrine level of <400 pg/ml, more patients with secondary adrenal insufficiency showed severe impairment than those without it. Secondary hypothyroidism, secondary hypogonadism, GH deficiency, and diabetes insipidus, on the other hand, were not significantly associated with prevalence of severe impairment of the epinephrine response. As the order of diminishing pituitary function associated with pituitary compression is GH before the other tropic hormones, with ACTH and TSH usually being the last hormones to show functional loss (17), our results seem to indicate that a spread of deficient pituitary hormones is associated with the severity of reduction in the epinephrine reserve. The activation of glucose counterregulation mechanisms starts with the sensing of hypoglycemia by the VMH to trigger the release of counterregulatory hormones (8–12). In rat experimental models, this counterregulation was found to be largely determined by the interaction between CRH receptor 1-mediated activation and CRH receptor 2-mediated suppression in the VMH (29). The sum total of these findings may lead the speculation that the balance between CRH receptors 1 and 2 is impaired in the VMH of most patients with pituitary adenoma and that the extent of this impairment is more severe in patients with a wider deficiency of pituitary hormones.

In contrast to plasma epinephrine, which is derived almost exclusively from the adrenal medulla, plasma norepinephrine, predominantly derived from sympathetic nerve endings acting as neurotransmitter, was within normal ranges at baseline in 18 of the 23 patients with pituitary adenoma. Norepinephrine responses to insulin-induced hypoglycemia were only marginal in these patients. Similar norepinephrine reserve to that in control subjects have been found in patients with 21-hydroxylase deficiency and/or with isolated glucocorticoid deficiency (24–26). However, increased norepinephrine secretion has been demonstrated in patients with Addison's disease (30) and in those who had undergone bilateral adrenalectomy (24), suggesting that some compensatory increases occur during sympathetic nerve activity. Similar compensation in basal sympathetic nerve activity may also occur in patients with pituitary adenoma.

In this study, we show for the first time that impaired epinephrine secretion in response to insulin-induced hypoglycemia is frequently observed in patients with pituitary adenoma. From the present study and the previous studies on patients with hypothalamic sarcoidosis or craniopharyngioma (14–16), defense mechanisms against hypoglycemia are thought to be disrupted to various extents in patients with pituitary or hypothalamic disorders. Defects in the secretion of GH and ACTH may be involved in failure to recover rapidly from hypoglycemia in patients who are deficient in these hormones. However, reductions in the epinephrine reserve may lead to defects in the defense against acute hypoglycemia in patients with pituitary and hypothalamic disorders, even though they may not show any pituitary hormone deficiency. Furthermore, the absence of the sympathoadrenal symptoms of hypoglycemia may confound a diagnosis of hypoglycemia.

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Cerebral motor control in patients with brain tumors around the central sulcus studied with synthetic aperture magnetometry

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Abstract. Synthetic aperture magnetometry (SAM) was applied to investigate changes in the mechanism of cerebral motor control in patients with tumors around the central sulcus in relation to the clinical relevance. MEG records were made during a resting state and a repetitive hand grasping task in patients with brain tumors around the central sulcus and in four control subjects. Topographic appearance of abnormal focal slowing in the delta, theta, and alpha bands ($N=10$) and event related desynchronizations (ERD) in the alpha, beta, and low gamma bands during the motor tasks ($N=6$) were analyzed statistically with SAM in relation to clinical signs and symptoms. Distribution of enhanced focal delta activity coincident with the motor cortices responsible for weakness. Volumetric analysis revealed emergence of tumor-related focal delta activity was greater for intra-axial tumors involving subcortical fibers than for other extra-axial tumors. In addition, patients with increased volume of enhanced delta activity exhibited poor functional recovery in the early post-operative period. Beta ERD in patients during affected side hand movement was also localized exclusively to the ipsilateral hemisphere contrary to the normal pattern. The characteristic focal delta distribution and the altered patterns of ERD in the patient group suggest not only close relation of cortical function and existing pathology but recruitment of diverse motor areas which may be required for the effective movement of the affected side.

Keywords: Magnetoencephalography; Synthetic aperture magnetometry; Brain rhythm; Event-related desynchronization; Hand motor physiology; Delta band; Brain tumor; Motor cortex; Sensory cortex

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1. Introduction

In slowly progressive brain tumors, impairment of motor function does not become apparent until a certain area of motor cortex or subcortical fibers is involved. Clinical observations of patients suggest that functional remodeling with neurophysiological dysfunction in the brain is taking place during the gradual growth of the tumor. For surgical treatment of tumors involving the motor areas, elucidation of this dysfunction or remodeling is important for pre-surgical planning and for effective rehabilitation.

The cerebral cortex including motor cortex exhibits oscillatory rhythms at rest [1], which can be modulated by pathological states as well as functional activation [2,3]. A recently developed synthetic aperture magnetometry (SAM) has been proved useful to estimate the tomographic distribution of the intensity of electrical activity within a selected band frequency, and its statistical derivatives from unaveraged MEG signal [4].

In this study, we applied SAM to evaluate the possible relation between the topographic distribution of focal slow-wave activity recorded by spontaneous MEG and the clinical symptoms and to study the power decrease in background brain activity during a motor task (event related desynchronization, ERD) in patients with brain tumors around the central sulcus.

2. Methods

Eighteen patients with brain tumors around the central sulcus and four control subjects were studied. Among them, 12 patients were evaluated on focal oscillatory activity (delta, theta and alpha bands) from the spontaneous MEG.

The areas displayed in SAM pZ image were assigned to four groups based on their locations in relation to the tumor: AC, adjacent to the tumor; EC, area lying over subcortical edema; IC, cortex ipsilateral to the tumor; and CC, cortex in the contralateral hemisphere. To assess whether the areas with high peak pZ values were located around the tumor, their peak pZ values in AC, EC and IC were compared with those for CC by the non-parametric Mann–Whitney U-test. Since the coverage of current source in the cortex by the sensor array was almost equivalent for each region of interest, we assumed pseudo-Z values could be comparable each other.

The rest of the patients (N=6) were examined on the motor evoked ERD. Subjects were instructed to undertake a trial consisting of six sessions of repetitive hand grasping of either hand for 10 s after 10 s of rest, keeping their eyes closed. The beginning and end of the movement was signaled to the subject by the investigator. The MEG data were acquired on trigger at the very end of the 10 s of grasping. Volumetric images of root mean squared source activity in each frequency band were generated by SAM method from the MEG data sampled before and after the trigger as control and active states, respectively. The statistical imaging is computed subsequently by comparing the power of both states on a single voxel basis using the Student t test. Only voxels displaying peak signal changes within each trial are collected. Images with a peak t value less than 2.5 or ERD distributed evenly over the hemisphere were excluded [2,3].

3. Results

In the normal subjects, consistent ERD in the sensorimotor cortex (MI/SI) contralateral to the hand movement was observed in the beta band. Those ERD were almost congruent

with hand representative area. Additional beta ERD was observed on the ipsilateral superior parietal lobule during dominant hand movement ($N=1$) and on the ipsilateral MI/SI ($N=2$), the contralateral inferior parietal lobule ($N=1$), and the superior parietal lobule and frontal operculum ($N=1$) during non-dominant hand movement. Low gamma ERD was observed in the contralateral MI/SI during dominant and non-dominant hand movement ($N=3$). In contrast, alpha ERD was observed over diverse regions of both cerebral hemispheres.

In the delta band, the statistical SAM pZ images clearly localized tumor-related focal oscillatory slow-wave activities to AC and/or EC, but not within the tumor in 11 of the 12 patients. The possible dysfunction at the identified locations was compatible with the main symptoms. Volumetric evaluation of this delta activity in AC and EC revealed that intensive were far more prominent in patients with intra-axial tumors, compared with those with extra-axial tumors. Enhanced delta activity within a large volume of cortex was noted around M1/S1 in the patients with poor functional outcome post-operatively.

In the theta band, the enhanced power observed in AC or EC was distributed more diffusely than in the delta band. In the alpha band, the power source was distributed bilaterally around the primary sensorimotor cortex. No consistent findings were obtained with respect to tumor location or presenting signs and symptoms.

For hand movement on the non-affected side, the beta ERD was observed on contralateral MI/SI and in the inferior parietal lobule (three and four subjects, respectively). For hand movement on the affected side the beta ERD was observed on ipsilateral MI/SI lateral to the assumed hand representative area ($N=4$), in the lateral pre-motor area ($N=2$), and in the inferior parietal lobule ($N=1$).

The low gamma ERD was observed in the contralateral MI/SI ($N=2$) and the pre-motor area during non-affected hand movement ($N=2$) and in the ipsilateral MI/SI during affected hand movement ($N=3$). The alpha ERD was observed in diverse regions without any strong consistency.

4. Discussion

In this present study, SAM analysis based on spontaneous MEG in patients with symptomatic brain tumors around the central sulcus revealed the presence of localized sources of delta-band activity in regions which corresponded to the presenting signs and symptoms in 11 of the 12 patients. Because the areas selected as "sources" consistently exhibited the highest delta activity they are likely to represent the most severely damaged regions. Therefore the positive correlation between the enhanced delta activity and the clinical symptoms indicates that the former represents a truly dysfunctional state. In fact, the distribution of areas with enhanced delta activities was heterogeneous within AC or EC, especially in patients with meningiomas. This indicates that the damage to surrounding tissues inflicted by tumors is highly variable and this may cause differences in clinical pictures.

Furthermore, patients with intra-axial tumors who manifested prominent subcortical edema and presented with more severe neurological symptoms and poorer surgical outcome, had a larger number of voxels with enhanced delta-band activity than patients with extra-axial tumors such as meningioma. It suggests that subcortical fibers, including thalamocortical fibers, are more impaired in patients with intra-axial tumors, which results in more prominent neurological deficits and emergence of enhanced delta-band activity.

These findings may indicate the difference in generators of tumor related slow-wave activity between intra-axial and extra-axial tumors [3].

The most prominent finding in motor evoked ERD study was the lack of beta ERD in the MI/SI contralateral to the hand movement on the affected side in the patients. This does not necessarily mean a lack of activity in the MI/SI, as ERD is a reflection of the modulation on basic rhythm by a motor event. Thus if the basic rhythm were suppressed in the resting state owing to the presence of the tumour and the surrounding edema, the ERD would not become apparent.

The beta band power attenuation in sensors on the affected side in the resting state, in comparison with the non-affected side, would provide evidence for the basic rhythm alteration in the tumour bearing hemisphere, making the above mentioned hypothesis plausible. Nevertheless, the ipsilateral ERD during affected hand movement would suggest that considerable mobilization of the ipsilateral motor areas is mandatory to maintain appropriate motor function [2]. This suggests that the affected motor cortex does not function fully in the normal range even at the stage when the motor impairment is not apparent at all, as was the case in most of the patients studied. The application of diffusion tensor imaging would be further step to study the influence of cortical and subcortical involvement to the lack of beta ERD in the affected motor areas and increased delta activity.

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