Time course of focal slow wave activity in transient ischemic attacks and transient global amnesia as measured by magnetoencephalography

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In this longitudinal study multichannel MEG was used to localize and to quantify focal pathological spontaneous neuromagnetic activity in six patients with transient ischemic attacks (TIA) and two patients with transient global amnesia (TGA). Slow (2-6Hz) and beta (14-30Hz) activity were monitored up to 10 weeks. Results were compared with normative data, and changes over time were statistically analyzed. MEG detected pathological activity that persisted clinical symptoms. Focal slow activity originating from sensorimotor (TIA) and mesiotemporal (TGA) cortices exceeded normal values up to 14 times during the first hours after the attack and recovered to normal within 11 days. Focal beta activity was not useful to monitor the time course of TIA or TGA.

INTRODUCTION

Transient ischemic attacks (TIA) are brief, reversible episodes of focal ischemic neuronal disturbance lasting maximally 24 hours by definition. It is generally accepted that TIAs can be considered precursor signs of stroke. They are intimately related to embolization of fibrin-platelet material due to atherosclerotic vascular stenosis in the majority of cases, and may involve any cerebral or cerebellar artery. The leading cause of TIAs, and ischemic strokes in general, is the embolization from the internal carotid artery [1]. Since there are no morphological changes visible in brain tissue on CT or MRI, the diagnosis relies on clinical examination, analysis of risk factors and detection of vascular stenoses by duplex sonography. None of these diagnostic tools provide a measure of brain function. However, there are methodological approaches to visualize the ischemic functional impairment of the brain during TIA using diffusion-weighted MRI (DWI) [2] or SPECT [3].

Transient global amnesia (TGA) is a benign disturbance in brain function characterized by anterograde and variable retrograde amnesia commonly accompanied by repetitive questioning that resolves mostly within 24h. It is generally believed that TGA is of vascular origin. Pathological findings during TGA were discovered in the mesio-temporal lobes using different neuroimaging methods including PET [4], SPECT [5] and DWI [6].

MEG localizes neuromagnetic activity related to cerebral dysfunction with high spatio-temporal resolution [7] and has mainly been used for evoked field recordings [8]. Vieth et al. [9] first localized pathological neuromagnetic focal slow activity associated with cerebral ischemia, a finding which has been confirmed by others [10]. In manifest stroke focal slow activity exceeded the average values of normal individuals by up to four times [11]. These MEG findings support the results of numerous EEG studies, partly dating back to the 1960s, where ischemic strokes were found to be accompanied by pronounced irregular and very slow delta activity [12]. With computerized quantitative EEG data analysis Pfurtscheller et al. [13] detected abnormalities in acute cerebral ischemia, including asymmetries of the rolandic mu-rhythm. Kappelle et al. [14] observed...
focal slow delta activity and alpha/mu asymmetries in lacunar strokes. With regard to TGA most workers in the
field agree that the majority of patients present with normal EEG, both during attacks and during asymptomatic
intervals [15]. However, data on long term changes in neuronal dysfunction after TIA or TGA are not available
Based on preliminary data [16], we hypothesized that MEG changes in TIA and TGA may exceed clinical
symptoms by at least up to 2 weeks. To detect possible long-term changes we extended the observation period
in this study up to 10 weeks. This is to our knowledge the first study to investigate long-term changes in human
brain function related to TIA and TGA and to prove the value of serial MEG measurements in monitoring the
time course of focal pathological activity accompanying transient neuronal dysfunction.

MATERIAL AND METHODS
Six TIA and two TGA patients (six males, two females, aged 44-82 years) were included in the study after
giving their written informed consent to the study protocol approved by the local ethics committee. The
diagnoses and clinical data of all patients are listed in Table 1. Serial multichannel MEG was performed in a
magnetically shielded room (Vacuumschmelze, Germany) using a 2 X 37 channel biomagnetic system
equipped with first-order gradiometers (MAGNES 11, Biomagnetic Technologies Inc., USA) 4 days (1st
measurement), 11 days (2nd measurement), 4 weeks (patients 3, 4, 7, 8) and 8-10 weeks (patients 1, 2, 5, 6, 8;
3rd measurement) after onset of clinical symptoms. Patient 4 presented with a further TIA on day 86 and was
additionally investigated only 4h after clinical symptoms had occurred. Patient 8 had four further TIAs within
76 days. Thrombendarterectomy could not be performed, since he refused to give his consent to invasive
measures. The last measurement of patient 4 and all data of patient 8 were excluded from statistical analysis.
Table 1 provides detailed information on the measurement protocols. Normative data were obtained using the
same measurement protocol from an age-matched group of eight healthy controls with no history of
neurological or psychiatric diseases (four males, four females, aged 50-66 years). In all patients cranial
anatomical T1 and T2 weighted MRI was obtained at 1.5T (Magnetom, Siemens, Germany) at the time of the
initial and last MEG measurements showing no ischemic lesions as evaluated by an experienced
neuroradiologist.

Table 1. Six TIA and two TGA patients, diagnoses and clinical symptoms, measurement intervals and anatomical correlates of focal pathologic slow and beta neuromagnetic activity.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Diagnosis</th>
<th>Measure. on day no</th>
<th>Clinical symptoms</th>
<th>MEG localization (bp 2-6 Hz)</th>
<th>MEG localization (bp 14-30 Hz)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>1st</td>
<td>2nd</td>
<td>3rd</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>single</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01</td>
<td>TIA right hemisphere</td>
<td>4</td>
<td>11</td>
<td>68</td>
<td>hemiparesis and dysesthesia left hand/face</td>
</tr>
<tr>
<td>02</td>
<td>TIA left hemisphere</td>
<td>4</td>
<td>11</td>
<td>60</td>
<td>mild paresis right hand, aphasia</td>
</tr>
<tr>
<td>03</td>
<td>TIA right hemisphere</td>
<td>4</td>
<td>11</td>
<td>32</td>
<td>sensory loss left arm/face</td>
</tr>
<tr>
<td>04</td>
<td>TIA left hemisphere</td>
<td>4</td>
<td>11</td>
<td>33 (86°)</td>
<td>monoparesis right arm, aphasia</td>
</tr>
<tr>
<td>05</td>
<td>TIA left hemisphere</td>
<td>4</td>
<td></td>
<td>60</td>
<td>hemiparesis and dysesthesia left hand/face, aphasia</td>
</tr>
<tr>
<td>TGA</td>
<td>single</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>06</td>
<td>TGA</td>
<td>4</td>
<td>11</td>
<td>67</td>
<td>anterograde amnesia, repetitive questioning</td>
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<tr>
<td>07</td>
<td>TGA</td>
<td>4</td>
<td>11</td>
<td>31</td>
<td>antero- and retrograde amnesia, repetitive questioning</td>
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<tr>
<td>TIA</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>08*</td>
<td>TIA left hemisphere</td>
<td>7, 14, 21, 32, 41, 47, 65, 76</td>
<td>hemiparesis and dysesthesia right hand/face, aphasia</td>
<td>Sensorimotor cortex left</td>
<td>Sensorimotor cortex left</td>
</tr>
</tbody>
</table>

* Excluded from statistical analysis.

Spontaneous neuromagnetic brain activity was recorded in data sets of 600 s duration from both hemispheres
simultaneously at a sampling rate of 520.8 Hz. Online highpass (1.0 Hz) and lowpass (100.0 Hz) filters were
applied, and an ECG was recorded. Patients and volunteers kept their eyes closed and had their heads fixed between both dewars covering major parts of both hemispheres. Both TGA patients had an additional measurement with a single dewar centered above the vertex. Accessible parts of the heads surface were digitally scanned in the MEG recording position (Isotrack 3D-digitizer™, Polhemus Inc., Colchester, USA).

![Fig. 1](image)

Fig. 1. (a,b) DDP results of focal slow neuromagnetic activity (2-6Hz) afterTIA (patient 1, a) and TGA (patient 6, b) superimposed on the corresponding MRI slices as isocontour lines. 1st measurement: day 4, 2nd measurement: day 11, a-2: Pseudo 3-D plots of the dipole distribution in the slice of maximal dipole densities of patient 1. Marked reduction from 1st to 2nd measurement.

Offline data analysis was performed as described previously [17,18]. After an initial 50 Hz notch filter, the magnetic field noise of the heart was removed by an ECG triggered digital noise reduction. All raw data sets were carefully checked for artifacts from eye and body movements, and affected sections were excluded from analysis. Digital bandpass-filters (bp) were applied to analyze the slow (bp 2-6 Hz) and beta (bp 14-30 Hz) frequency bands separately. A principal component analysis (PCA) was used to select a minimum of 10 s from the whole measurement where one component predominated the signal. This was achieved by analysing overlapping time sections with a length that corresponded to the mean signal frequency included. In those selected time sections the dominant component typically described > 95 % of the signal variance. For those

<table>
<thead>
<tr>
<th>Bp 2-6 Hz</th>
<th>DDP max</th>
<th>D total</th>
<th>DDP max/t</th>
</tr>
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<tr>
<td>Mann-Whitney U-test</td>
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<td></td>
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</tr>
<tr>
<td>1st measurement vs norm</td>
<td>0.005</td>
<td>ns</td>
<td>0.0022</td>
</tr>
<tr>
<td>2nd measurement vs norm</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>3rd measurement vs norm</td>
<td>0.048</td>
<td>0.039</td>
<td>0.039</td>
</tr>
<tr>
<td>Wilcoxon sum rank test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st vs 2nd measurement</td>
<td>0.0044</td>
<td>0.0058</td>
<td>0.0033</td>
</tr>
<tr>
<td>1st vs 3rd measurement</td>
<td>0.0033</td>
<td>0.0033</td>
<td>0.0033</td>
</tr>
<tr>
<td>2nd vs 3rd measurement</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Table 2. Statistical analysis of focal pathologic slow neuromagnetic activity: comparison to normative data (Mann-Whitney U-test) and to follow up measurements (Wilcoxon sum rank test) (ns = no significance).

time sections a single source model should be the adequate mathematical model. Therefore single equivalent current dipoles were calculated every 2 ms over the selected data segments using a locally fitted spherical head model. Only dipoles showing statistical correlations between estimated and measured magnetic field distribution of $p > 0.9$ were accepted for data evaluation. The spatial distribution of dipoles was determined by a 3D convolution with a Gaussian shaped envelope, with the variance considering the localization uncertainty of the individual dipole localizations yielding a dipole density plot (DDP) [19]. MEG localizations were
inserted in anatomical 3D T1-weighted images using a contour fit technique [11]. Spontaneous neuromagnetic activity, was quantified by calculation of the total dipole number selected by PCA and DDP (D_{total}), the concentration of dipoles within the area of highest dipole density (density maximum; DDP_{max}) and the normalized density maximum (DDP_{max}/t) [18]. MEG data were statistically correlated with normal controls (non-parametric Mann-Whitney U-test) and over time (Wilcoxon sum rank test). Differences with \( p < 0.05 \) were considered statistically significant.

**RESULTS**

In all six TIA patients pathological slow and beta activity focused reproducibly in the primary sensorimotor cortices of the hemisphere contralateral to the symptoms. Both TGA patients showed pathological neuromagnetic activity in mesial and basal aspects of the temporal lobes bihemispherically (Table I; Fig. 1a,b). In all eight patients slow activity exceeded normal values in the 1st, but not in the 2nd or 3rd measurement. Slow activity was significantly reduced from 1st to 2nd and 1st to 3rd investigation. No significant differences were observed between 2nd and 3rd investigation (Table 2; Fig. 2a,b). Pathological focal slow neuromagnetic activity therefore exceeded clinical symptoms at least up to 3 days (1st measurement, day 4) and decreased to normal within 11 days (2nd measurement). Two patients had one (patient 4) or four (patient 8) further monomorphic TIAIs during the follow-up period. Patient 4 was investigated four hours after clinical symptoms had disappeared: pathological slow activity exceeded normal values (mean DDP_{max}/t=35.63) up to eight times (4th measurement, DDP_{max}/t = 284.53; Fig. 3b). In patient 8 the intervals between onset of symptoms and MEG measurement varied between 3h (5th measurement DDP_{max}/t = 488.33; 14 times above normal) and one day (2nd measurement DDP_{max}/t=288.12; eight times above normal; Fig. 3c). Focal pathological beta wave activity did not significantly change over time. In concordance with slow foci, beta activity originated from sensorimotor (TIA) or temporal (TGA) cortices in each patient. Individual examples may demonstrate characteristic time courses of focal slow activity associated with transient neuronal dysfunction (Fig. 3a-c): typical time course of decreasing slow activity after a single TIA (patient 1, Fig. 3a); slow activity eight times above normal 4h after TIA (patient 4, Fig. 3b); repeated increases (up to 14 times above normal) and decreases of slow activity in multiple TIA (patient 8, Fig. 3c).

**DISCUSSION**

This study is to our knowledge the first longitudinal study of changes in pathological neuromagnetic activity after TIA and TGA. In all patients transient neuronal dysfunction was accompanied by pathological focal neuromagnetic activity that originated from the sensorimotor cortices contralateral to the clinical findings after TIA or from the temporobasal lobes bilaterally after TGA. Slow neuromagnetic activity showed an initial increase above normal 3 days after the attacks and a decrease to normal values within 11 days. In some cases a further decrease within the normal range could be observed up to 10 weeks. Both patients who suffered additional monomorphic TIAs during the follow-up period showed repeated increases of focal slow activity in the same localization related to each TIA that again decreased afterwards.
The finding of focal slow brain activity in the course of ischemic strokes, presenting within a few minutes after occurrence, is well known from EEG [15] and is used in clinical routine applications such as EEG monitoring during carotid artery revascularization [20]. In TIA, EEG changes (ipsilateral minor slow activity) have been reported during the attack [15]. In accordance with EEG, MEG has revealed pathological slow neuromagnetic activity in patients with hemodynamically relevant stenoses of the internal carotid arteries that normalized after endarterectomies [21]. MEG localized focal slow activity adjacent to ischemic brain lesions [9,10]. A bimodal investigation using MEG and MR spectroscopy [17] showed good spatial correlations of abnormal neuromagnetic activity and biochemical changes (reduced N-acetyl concentrations) in ischemic brain regions.

![Fig. 3](image)

**Fig. 3.** (a) Typical time course: initial increase of slow activity on day four (1st measurement, DDP_{max}/t = 59.1; 1.8 times above normal), significant reduction to normal until day eleven (2nd measurement, DDP_{max}/t = 25.7; 0.8 times of normal values). No significant changes during the further time course (3rd measurement, DDP_{max}/t=23.8; 0.73 times of normal values). (b) Marked increase early after the attack: second monomorphic TIA; initial increase of slow activity (1st measurement, 1.35 times above normal), typical further reduction (2nd and 3rd measurement), marked increase 4h after TIA (4th measurement, DDP_{max}/t=284.5; 8.7 times above normal). (c) Repeated increases and decreases of slow activity in multiple monomorphic TIA: normal values 1 week after initial TIA (1st measurement), marked increases after each TIA (2nd, 3rd, 5th, 7th measurements) up to 14 times above normal (5th measurement, DDP_{max}/t=488.3), decreases to normal values between each TIA (4th, 6th, 8th measurements).

The results of the initial measurement in our study demonstrated on the one hand that MEG is generally able to provide plausible source localizations of increased pathological brain activity in TIA patients. Since these measurements were performed three days after clinical symptoms had disappeared, this finding on the other hand supported the hypothesis that the restoration of normal neuronal function after transient cerebral ischemia may exceed the duration of clinical symptoms.

With respect to the results obtained from the two TGA patients, both statements hold for TGA as a transient neurological disorder of probably vascular origin as well. Both patients presented with bilateral pathological mesiotemporal and temporo-basal slow and beta neuromagnetic activity on day four. Their time courses showed a normalization of slow wave activity from 1st to 2nd measurement comparable to the TIA patients. EEG in TGA is typically normal, but PET and SPECT have shown unilateral or bilateral temporo-basal, striatal or thalamic hypoperfusion [5] resulting from transient ischemia in the posterior cerebral circulation [4]. Strupp et al. [6] also found bilateral pathological signals within the mesial temporal lobes, the diencephalon and the basal forebrain nuclei in DWI, a finding not supported by Gass et al. [22]. These abnormalities were partly found during, directly after (SPECT, DWI) or up to 14 days after the attacks (PET) and disappeared within 2 (DWI) or 4 weeks (SPECT, PET). Our results now indicate that neuronal dysfunction in TGA may also be characterized by pathological neuromagnetic brain activity.

We suggest that pathological neuromagnetic activity is a non-specific phenomenon associated with neuronal dysfunction. This assumption has been supported by previous MEG findings in patients with brain tumors [11] and multiple sclerosis [18]. Increased focal slow and beta activity was a common finding regardless of the
etiology of the disease. Nevertheless, we used measurements of spontaneous neuromagnetic activity in our study to analyze the time course of pathological changes, with respect to preliminary results [16]. An alternative (and perhaps more specific) approach was to use evoked activity (with regard to motor or memory function, respectively) for the longitudinal analysis, as it was used in EEG studies either in a task-related design using finger movement sequences of increasing complexity [23] or in an event-related design comparing movements in Parkinsonian patients before and after L-dopa administration [24]. However, even regardless of methodological problems concerning then needed performance control (especially in memory-related tasks in TGA patients), this approach did not appear to be applicable to patients with transient neurological disorders who were without clinical symptoms during the time of the measurement. In our patients pathological beta activity did not change significantly with time. We speculate that fast components (20 Hz) of the spontaneous rolandic mu-rhythm [25] may have altered pathological neuromagnetic activity in the beta frequency band. However, sources of pathological beta activity showed a good spatial agreement with the slow foci in all patients in the initial measurement and may therefore be a useful supplement to localize neuronal dysfunction related to transient cerebral ischemia.

CONCLUSION

MEG was useful to monitor neuronal dysfunction after TIA and TGA as reflected by focal pathological neuromagnetic activity in the sensorimotor cortices contralateral to the clinical symptoms (TIA) and the mesiotemporal lobes in both hemispheres (TGA). As proposed in the hypothesis, neuronal dysfunction persisted after clinical symptoms had disappeared. In all patients pathological focal slow neuromagnetic activity was characterized by an initial increase three days after the attack (mean 1.65 times above normal), that reached in clinical symptoms had disappeared. In all patients pathological focal slow neuromagnetic activity was characterized by an initial increase three days after the attack (mean 1.65 times above normal), that reached in individual cases values up to 14 times above normal within the first hours after the attack. This increase was followed by a decrease to normal values until day 11. Focal beta activity did not provide information on the individual cases values up to 14 times above normal within the first hours after the attack. This increase was characterized by an initial increase three days after the attack (mean 1.65 times above normal), that reached in individual cases values up to 14 times above normal within the first hours after the attack. This increase was followed by a decrease to normal values until day 11. Focal beta activity did not provide information on the time course of neuronal dysfunction after TIA or TGA.

REFERENCES