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Simultaneous Recording of Event-Related Auditory Oddball Response Using Transcranial Near Infrared Optical Topography and Surface EEG

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Near infrared optical topography (OT) is the measurement of hemoglobin absorption simultaneously from an array of optical fibers on the scalp to construct maps of cortical activity. We demonstrate that OT can be used to simultaneously detect and characterize the hemodynamic responses associated with an "oddball" auditory stimulus and that corresponding electrical event related potentials can be acquired simultaneously using conventional scalp recordings. In addition to the measured electrical response, the hemodynamic localization is consistent with fMRI studies, which show significant activation in the temporal and parietal cortical regions. The event-related response of total hemoglobin showed relatively slow peak latencies (5.8 ± 0.3 s), which were also consistent with fMRI. The current study shows the regions of peak hemodynamic activity that are in closest proximity to areas of peak electrical activity. This is the first demonstration of simultaneous ERP electrical recording and non-invasive optical mapping in human subjects, which promises to be an important tool in the characterization of both normal and abnormal brain function.

INTRODUCTION

Event related (ER) monitoring of hemodynamic responses offers several advantages over block design techniques in neuroimaging (Robson *et al.,* 1998). Previous ER-fMRI studies have identified brain regions that are activated in response to infrequent "oddball" stimuli, which elicit a characteristic ER potential, the P300, that is prominent in the central-parietal (Pz) region of the scalp when measured with surface electrodes (Donchin, 1980; Sutton *et al.,* 1965). Characteristics of this response, such as latency and amplitude have been used to assess effects of aging, psychiatric disorder, and memory performance. Various factors in the design of oddball paradigms may influence the amplitude and latency, but it is not clear how changes in electrical activity affect changes in blood flow and metabolism. Simultaneous recording or ERP and the corresponding hemodynamic response would be of considerable interest, and much effort to combine ERP and fMRI is underway.

It has long been known that light transmission and absorption in living tissue is sensitive to hemoglobin concentration and oxygenation state (Milliken, 1933). In neuroscience applications, the imaging of reflected light as a measure of neural activity has a widespread use in the investigation of functional architecture of the cortex (Frostig *et al.,* 1990, Mayhew *et al.,* 1998). Transcranial near infrared spectroscopy (NIRS) allows the non invasive differentiation between tissues with different absorption or scattering properties and can provide spectroscopic information on chromophore concentrations such as oxy- and deoxyhemoglobin and cytochrome oxidase (Jobsis, 1977; Hebden and Delpy, 1997). NIRS has been successfully employed to monitor global brain oxygenation changes associated with hypoxia (Cope and Delpy, 1988) and local hemoglobin oxygenation changes associated with neural activity (Chance *et al.,* 1993; Kato *et al.,* 1993; Villringer *et al.,* 1993; Hoshi and Tamura, 1993). NIRS has been used to record motor activation using both block design and a single trial paradigms (Obrig *et al.,* 2000), it should be well suited to detect responses to other event related stimuli. Near infrared optical topography (OT) was proposed as a new method for visualizing brain activity (Maki *et al.,* 1995) by using an array of optical fibers to obtain a spatial map of absorption changes using light reflected from the cortical surface. Optical topography devices have been used to monitor spatio-temporal blood volume and oxygenation changes in cortex during sensory stimulation (Maki *et al.,* 1996; Watenabe *et al.,* 1998), cognitive function (Koizumi *et al.,* 1999), and epileptic seizures (Watenabe *et al.,* 2000), and it makes possible noninvasive measurements of human brain function under a variety of conditions with little subject restriction. Furthermore, since the optical probes are non-metallic and require no electrical coupling to

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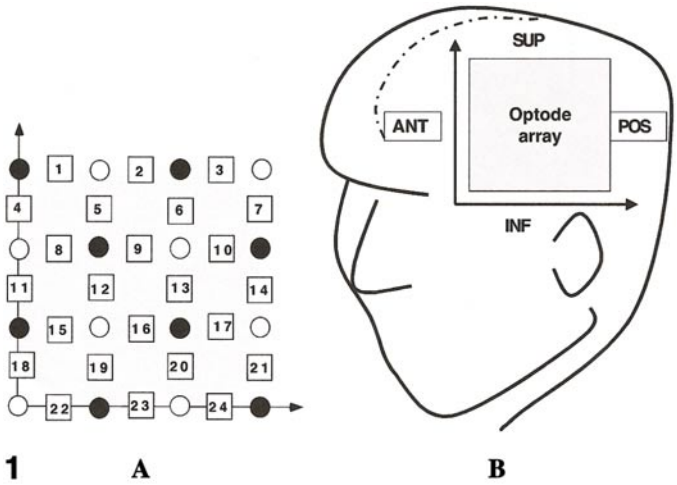

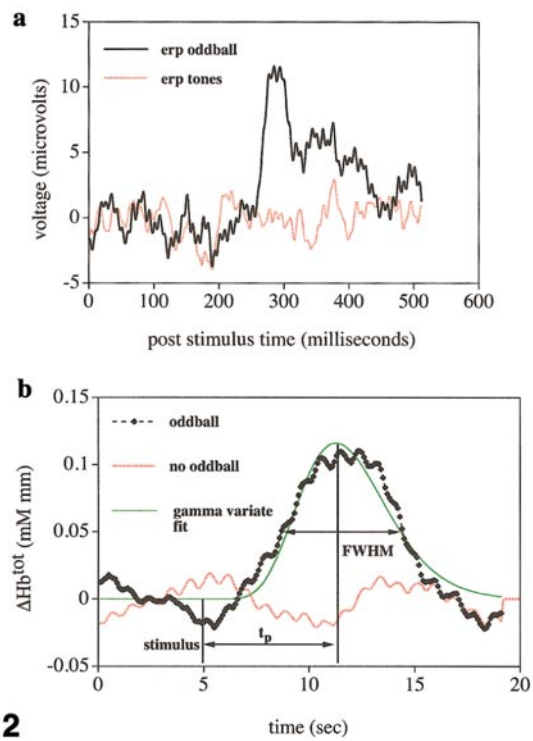

FIG. 1. (A) Optode arrangement. Open circles denote incident fibers, filled circles denote detection fibers, and numbers refer to the effective optode position for each fiber pairing. (B) Array positioning on the head; posterior, anterior, superior, and inferior orientations are illustrated.

FIG. 2. Single subject averaged timecourses for oddball response: (a) electrical ERP and (b) OT total hemoglobin. Solid lines denote oddball tone, dotted lines denote continuous tones (no oddball). The oddball tone is presented at $t = 5$ s in the OT timecourse.

the subject, measurements can be performed simultaneously with EEG, fMRI, and MEG.

The use of imaging techniques to localize electrical responses in the brain has proven fruitful, but the simultaneous recording of electrical responses can often be problematic in fMRI due to strong coupling between the time varying imaging field gradients and the EEG electrodes, which can generate currents that are much greater than the underlying bioelectric signals. The optical system can, in principle, provide an excellent means for localizing electrical activity in cortex and for recording corresponding hemodynamic changes with high temporal resolution (~100 ms). The purpose of this study is to demonstrate the ability of OT to detect the hemodynamic response associated with an auditory "oddball" task which generates a well known electrical response, the P300 (Donchin, 1980; Sutton *et al.*, 1965), and which is widely used in neurological and psychiatric evaluations of clinical subjects.

METHODS

Task

Simultaneous optical and electrical recording was performed on 5 subjects (4 male, 1 female). Computer generated auditory stimuli (PsyScope and Sound Sculptor II) were presented to the subjects via headphones. Auditory stimuli consisted of 1000 Hz tones of 100 ms duration with an interval of 1.5 s between tones, while the rare "oddball" tone was a 1500 Hz tone of the same duration. The oddball tones were presented at 8% of the total number of tones, which gives an average inter stimulus interval of 19 s (chosen conservatively to ensure hemodynamic responses returned to baseline). Each experimental block consisted of 12 oddball tones. Three to four blocks were averaged in each experiment for a total of 36–48 ERPs and total exam time of 12–15 min.

Optical Mapping

Near infrared optical topography was performed using a 48-channel spectrometer operating at 780 and 830 nm (Hitachi ETG-100), which is capable of mapping 24 cortical regions simultaneously (Maki *et al.*, 1995; Koizumi *et al.*, 1999). Total hemoglobin changes were mapped over a 9×9 cm area covering a portion of the left hemisphere. Figure 1 shows the arrangement of the eight incident and eight detection fibers on the surface of the skull. Fibers are mounted on a plastic helmet which is fitted to the subject and held by adjustable straps. Each pair of adjacent transmission and detection fibers define a single optode unit. Open circles denote incident fibers, filled circles denote detection fibers and numbers refer to the effective measurement position for each fiber pairing, which yields 24 optodes in this configuration. The measurement positions correspond to regions of optimal light penetration. In order to obtain the optode signals simultaneously, each transmission fiber is frequency modulated, and the detected signals are passed through lock-in amplifiers to

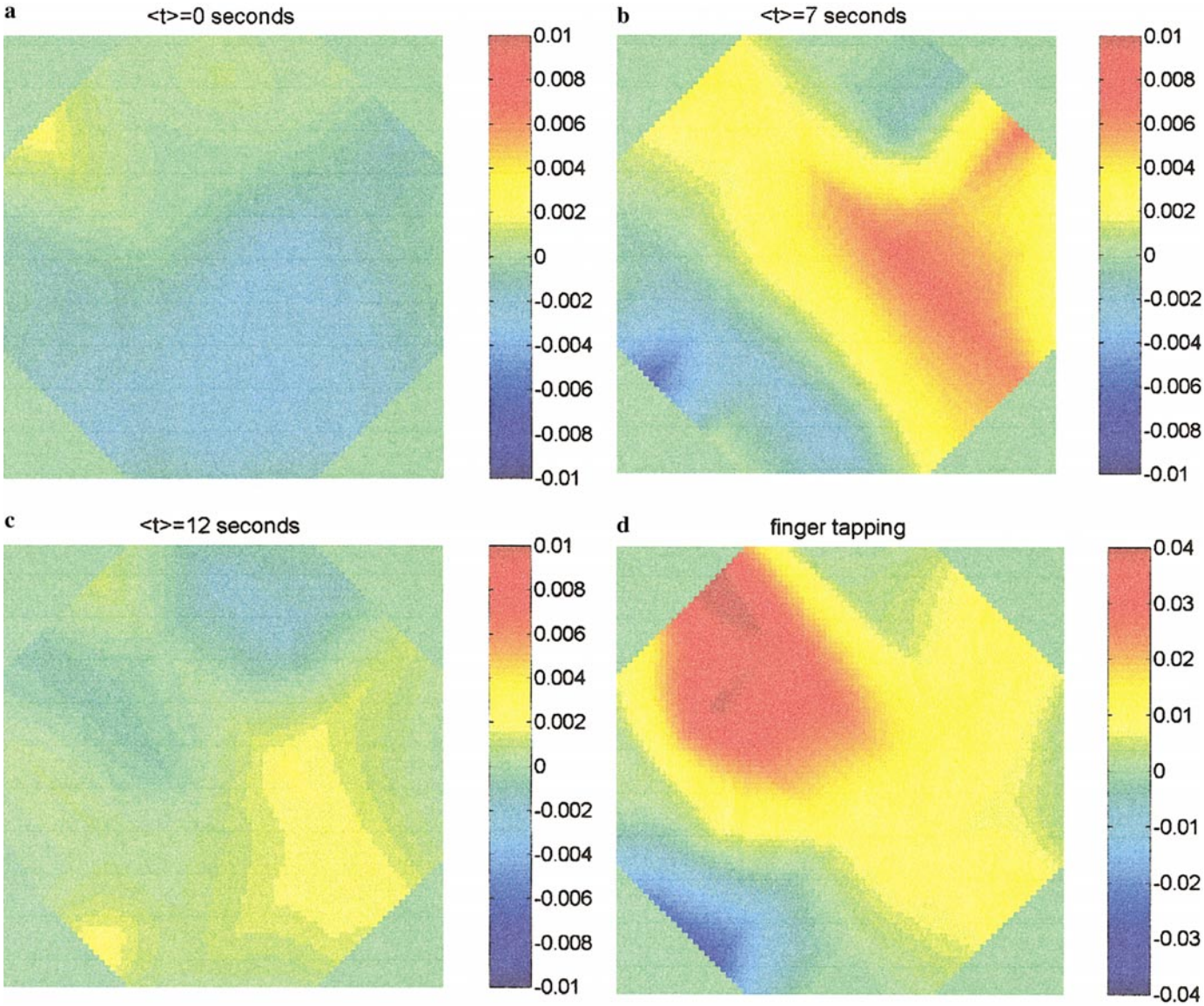

FIG. 3. (a, b, c) Single subject OT maps showing 5-s epochs of event related auditory oddball response as a function of post stimulus time. The oddball maps are evaluated at average times of (a) 0 s, (b) 6 s, and (c) 12 s post-oddball tone. (d) Block averaged primary motor response. Areas of total hemoglobin increase are denoted in red with separate colorbars for oddball (c) and motor (d) responses.

avoid crosstalk. High temporal resolution (100 ms) is possible since simultaneous detection of frequency modulated laser signals does not require optical switching (Maki *et al.*, 1995). By measuring the optical absorption data at two wavelengths during stimulation the hemodynamic parameters can be determined for each optode position to generate a two dimensional map. This map is then interpolated to produce the final optical image. The interfiber spacing is ~3 cm, which is considered sufficient to ensure cerebral penetration of the optical path while maintaining good sensitivity (Hebden and Delpy, 1997). Further details of the experimental apparatus and procedure are given elsewhere (Maki *et al.*, 1995, 1996; Koizumi *et al.*, 1999).

The spectrometer was gated to the tone generation computer for proper signal analysis. Data were averaged in epochs for each oddball tone which consisted of 5–8 s of signal in the pre stimulus period and 15 s of signal in the poststimulus period to account for the anticipated slow hemodynamic response times as indicated in previous NIRS (Obrig *et al.*, 2000) and fMRI (Robson *et al.*, 1998) studies. The signal from each tone epoch was linearly baseline corrected to avoid drift. In order to localize the relative position of the oddball activation, each subject also performed a motor task to identify primary motor cortex (Maki *et al.*, 1996; Kleinschmidt *et al.*, 1996; Chance *et al.*, 1997; Obrig *et al.*, 1996; Kennan *et al.*, 2000). A block design paradigm

was employed where four repetitions of 20 s of right-handed finger tapping (~2 Hz) were interspaced between 30-s rest periods.

ERP Recording

Data were collected from five subjects on a computer with SynAmp amplifiers (Neurosoft Inc). Previous studies using conventional 10–20 array have shown most robust recording occurs at Pz. For these exploratory studies, a single scalp electrode with earlobe reference was placed in Pz. Signals were averaged in epochs (−200–824 ms) and individually baseline corrected. The acquisition was performed in AC mode at a frequency of 500 Hz. High pass and low pass filters were set to 0.05 and 100 Hz respectively, while a notch filter was set to 60 Hz.

RESULTS

Temporal Response

Figure 2 shows the timecourses for the simultaneous electrical and optical responses in a single subject. In general we found that the optical probes introduced little interference to the EEG scalp electrode. Under typical experimental conditions, with the optical probes and EEG electrodes in place, we found that the standard deviation of the baseline corrected EEG signal during rest increased by less than 3% when the optical spectrometer was on relative to when the machine was off. This noise increase was well within tolerence levels for these experiments. Figure 2a shows the EEG response at PZ during continuous tones (dotted line) and after the oddball tone (solid line), which is consistent with a P300 waveform (Donchin, 1980; McCarthy *et al.,* 1997; Menon *et al.,* 1997). While a single scalp electrode is not sufficient to fully characterize the P300 response we note that the single scalp electrode result is consistent with our previous findings using the same task with a larger electrode array (Horovitz *et al.,* 2000). Figure 2b shows the corresponding changes in total hemoglobin, ΔC_{tot}, (mM mm) for the same task showing the clear response to the oddball tone. The timescales of Figs. 2a and 2b differ by a factor of 50 in order to appreciate the temporal differences between the electrical and hemodynamic responses. For reference, the oddball tone is presented at $t = 5$ s in Fig. 2b. It should be noted that units for the total hemoglobin are relative since the optical pathlength of the scattered light was not determined (Hebden and Delpy, 1997; Obrig *et al.,* 2000; Maki *et al.,* 1995). In each subject, the total hemoglobin response to the oddball tone was not localized to a single optode, therefore the timecourses were averaged over all regions which showed positive responses. This included the optode of maximum response and several neighboring optodes.

TABLE 1

Group Averaged ($N = 5$) Hemodynamic Response Times and Peak Position Relative of Motor Cortex

Total Hb response Time to peak, t_p	Total Hb response Full width at half max, FWHM, (s)	ΔX_{rel}, relative to motor cortex (mm)	ΔY_{rel} relative to motor cortex (mm)
5.8 ± 0.2 s	5.9 ± 0.3 s	−18 ± 9 mm	21 ± 8 mm

Note. Position is defined as, ± = inferior/superior (X), anterior/posterior (Y). Errors denote standard deviations of group averages.

In the case of continuous tones there was no appreciable response observed. This is probably because the interval between identical tones (1.5 s) is much faster than typical hemodynamic response times (5–10 s) and therefore generate a steady state of blood flow in auditory cortex. In order to characterize the temporal features of the hemoglobin data, a gamma variate function (Robson *et al.,* 1998) was fit to the oddball timecourse, which yielded the time to peak response and width at half maximum. The temporal features of the total hemoglobin response were not particularly sensitive to the choice of threshold. As shown in Table 1, the hemodynamic changes are slow relative to the electrical activity with a peak delay of 5.9 ± 0.3 s averaged over all subjects. The average duration of the hemoglobin changes in all subjects, as measured by half width, was 5.8 ± 0.2 s.

Spatial Response

Figure 3 shows a map of relative total hemoglobin response during the auditory oddball task (Figs. 3a–3c) and the motor localization task (Fig. 3d). The maps depict 9 × 9-cm areas of the left hemisphere as described in Fig. 1. The magnitude of the hemoglobin responses during the auditory oddball were determined by integrating the timecourse over 5 s epochs centered at 0 s, 7 s, and 12 s poststimulus. The early time map illustrates the level of spatial fluctuations in the hemoglobin signal, while the map at 7 s shows the delayed and localized response to the oddball tone, and the map at 12 s shows the slow decay of the vascular response. Figure 3d shows the topographic map for the motor task in the same subject. Figures 4a and 4b show the peak total hemoglobin response maps for the oddball and motor tasks overlaid on the brain surface for clarity. The registration was roughly determined by projection of the OT helmet onto the brain surface and is intended only for illustrative purposes. The areas of positive total hemoglobin activation are denoted by the red regions. An increase in total hemoglobin is consistent with an increase in blood volume and blood flow as observed during periods of enhanced neuronal activity

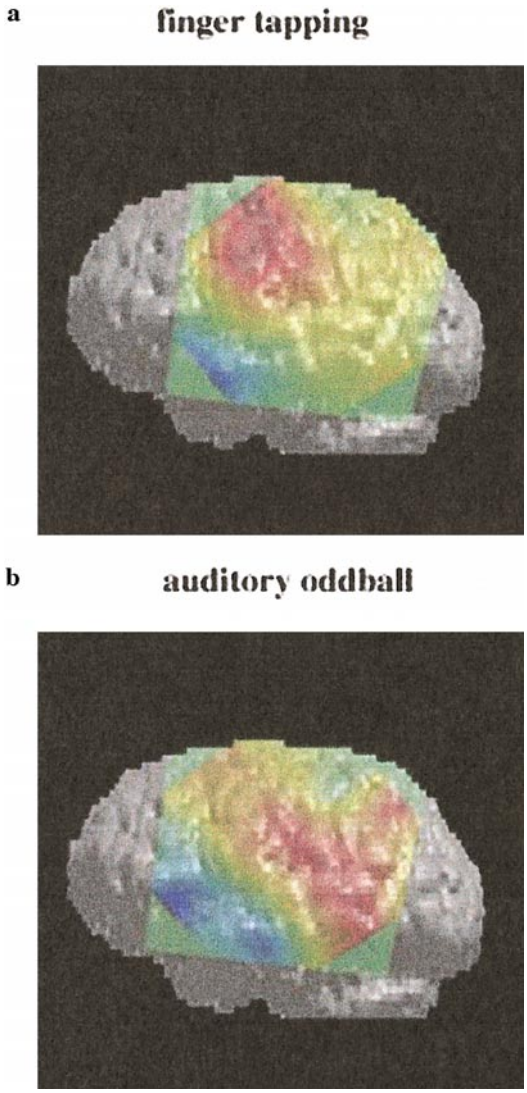

FIG. 4. Single subject data overlaid onto brain surface: (a) Primary motor response (b) peak auditory oddball response. Areas of total hemoglobin increase are denoted in red.

(Obrig *et al.*, 2000; Mandeville *et al.*, 1998; Kennan *et al.*, 1998). For the subject shown, the peak region of oddball activation is somewhat posterior and inferior to the motor cortex. In order to quantify the relative position of the oddball activation the center of mass of the total hemoglobin response was calculated for a large region of interest, which encompassed the areas of significant response. Table 1 shows the averaged results for all subjects. The area of peak total hemoglobin response to the oddball stimuli was 18 ± 9 mm posterior and 21 ± 8 mm inferior to the motor cortex. This yields a radial distance of approximately 27 mm, which corresponds to ~1 optode displacement for the OT configuration used in this study. The posterior and inferior displacement relative to motor cortex is consistent with the position of supramarginalis gyrus (area 40 of the parietal lobe) (Talairach and Tournoux, 1988), though further fMRI studies would be required to validate the precise source.

DISCUSSION

The event related total hemoglobin response is similar to that observed in fMRI studies (McCarthy *et al.*, 1997; Menon *et al.*, 1997; Optiz *et al.*, 1999; Stevens *et al.*, 2000; Yoshida *et al.*, 1998; Le *et al.*, 2001). Recent fMRI studies using similar gamma variate fitting have shown hemodynamic delays in the BOLD response of 4.5–4.9 s with a FWHM of ranging from 3.9–4.3 s (Le *et al.*, 2001). The slower total hemoglobin response observed in this study is consistent with observations of slow blood volume response relative to BOLD (Mandeville *et al.*, 1998). The optical response may also appear slower since the optical signal is integrated over a relatively large region. With regards to spatial localization, the observation of activation which was posterior and inferior to the motor cortex is consistent with previous fMRI results which showed significant oddball activation in temporal/parietal regions (McCarthy *et al.*, 1997; Optiz *et al.*, 1999). There may of course be other regions which contribute significantly to the hemodynamic and electrical auditory oddball response which could not be detected by the current configuration, which include prefrontal and occipetal regions (Horovitz *et al.*, 2000, 2001). This can be confirmed by further studies with the optical helmet and scalp electrodes centered on different regions.

CONCLUSIONS

We have shown that near infrared optical topography in conjunction with EEG can be used to record hemodynamic and electrical responses simultaneously during an event related task. This study demonstrates the feasibility of using combined electrical and optical recording to characterize ER responses. These techniques can be extended to the examination of other ER responses, which have been shown to be markers of cortical dysfunction. It is anticipated that such integrated mapping will become will provide an important means to classify neuronal and metabolic changes in the brain.

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