Simultaneous intracerebral EEG recordings of early auditory thalamic and cortical activity in human

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Abstract

We describe documented simultaneous intracerebral auditory evoked potentials from the auditory cortex and medial geniculate body (MGB) of a human patient. The MGB response lasted >300 ms, with an initial negativity at 13.5 ms (N13), two positive peaks P21 and P29, and two broader negativities N50 and N200. P21 and N50 amplitudes were strongest for lowest tone frequencies, suggesting possible MGB tonotopic organization. Thalamic peaks were strongly interlaced with cortical activities recorded in Heschl's gyri before 30 ms: N13 preceded the first cortical component by 3.5 ms, then P21 and P29 preceded and lagged, respectively, the following two cortical polarity reversals by 1.5–2 ms. This study provides new functional data on the human MGB, and supports a more complex than simply relay-like role of the thalamus in sound perception.

Introduction

Although extensively studied in animals, there is a deep lack of functional data on the human medial geniculate body (MGB). The human MGB has been anatomically described by Winer (1984) and its well established contribution to auditory perception mainly relies on stereotactic stimulation of the thalamus (Tasker & Organ, 1973; Velasco et al., 1982), functional imaging studies (Guimaraes et al., 1998) and studies of patients with MGB lesions showing impairment of auditory perception (Fukutake & Hattori., 1995) or abnormal auditory cortical activity (Fischer et al., 1995). This deep and inaccessible structure cannot be recorded on a millisecond time scale using noninvasive techniques such as electroencephalography (EEG) or magnetoencephalography. Intraoperative subcortical EEG has mainly probed the vicinity of the inferior colliculus (Moller & Jannetta., 1982), and studies reporting electrophysiological thalamic data are rare, usually not clearly documented, and obtained with narrow analysis time windows not allowing a complete observation of the full MGB activity (Hashimoto et al., 1981; Velasco et al., 1982).

This paper reports simultaneous intracerebral EEG recordings of the human MGB and auditory cortex serendipitously obtained in an epileptic patient, with the aim of highlighting the dynamics of the human MGB and the temporal correspondence of early thalamic and cortical activities. Parts of these data have been published in abstract form (Yvert et al., 2001).

Materials and Methods

Anatomical locations of intracerebral recording sites

Auditory evoked potentials (AEPs) were recorded using deep multicointact electrodes stereotactically implanted in a right-handed epileptic patient (female, aged 26) undergoing presurgical evaluation of a left pharmaco-resistant tempo-mesial epilepsy. The patient T1-weighted 3-D magnetic resonance images (MRIs) (pixel size 1.27 mm) were acquired prior to implantation. Angiography was used to determine the target electrode positions in Talairach space as described by Musolino et al. (1990). However, these target positions differed from the actual final positions within the range of stereotactic accuracy. We thus again coregistered, a posteriori, the electrode positions available from two orthogonal sagittal and coronal X-ray radiographs obtained after implantation onto the MRIs. First, the bone contour of the mid-sagittal MRI was matched to that of the sagittal X-ray radiograph, providing antero-posterior and inferior–superior coordinates. Then, medio-lateral coordinates were obtained on the coronal X-ray radiograph. The registration precision was evaluated as <2 mm in another patient for whom MRIs, acquired <24 h after electrode removal, still showed electrode tracks.

One electrode (‘H’, Fig. 1a) had deep contacts within the postero-medial portion of the first and second Heschl’s gyri, a region housing the primary auditory cortex (Liégeois-Chauvel et al., 1991; Rademacher et al., 1993). At the tip of another electrode (‘C’) aiming at the tail of the left hippocampus, the two deepest contacts C1 and C2 appeared to be located at the level of the MGB and lateral geniculate body (LGB). Although thalamic structures are difficult to delineate on T1-weighted MRIs, the approximate locations of the MGB is indicated in Fig. 1b, based on atlases of the human brain and thalamus (Mai et al., 1997; Morel et al., 1997) and anatomical findings of Fujita et al. (2001).

Next, we determined anterior and posterior commissures on the MRIs and registered the thalamic contacts onto the atlas of the thalamus published by Morel et al. (1997). While C1 was registered
on the lateral border of the MGB, C2 was located in the LGB (Fig. 1c).

A further convincing confirmation of the thalamic electrode locations was obtained functionally (Fig. 1d): auditory stimuli elicited reproducible responses only on C1, while visual stimuli elicited the strongest responses on C2 spreading to C1 by volume conduction (similar shape and lower amplitude). These recordings were consistent with C1 being located between MGB and LGB, with C2 being more lateral at the level of the LGB.

**Experimental paradigms**

Auditory stimuli were delivered to the contralateral right ear at 60 dB SL (sensation level) above hearing threshold while the patient was watching a silent movie. This patient reported no auditory complaints, and gave informed consent to undergo these routine clinical recordings serving as preoperative cortical functional mapping and being approved by the ethical committee of the Neurological Hospital. In a first paradigm investigating possible tonotopic effects, AEPs were obtained for short pure tones (3 ms rise time, 20 ms plateau, 20 ms fall time) of five different frequencies (250, 500, 1000, 2000 and 4000 Hz) delivered every 500–700 ms (random) in 10 randomly intermixed blocks of 200 identical stimuli. Continuous signal was filtered (0.3–200 Hz), digitized at 1 kHz and averaged. To better probe weakest and highest-frequency components, a second paradigm used a higher sampling rate (2 kHz) and a higher number of stimuli (1000 1-kHz tones with 3 ms rise/fall times and 50 ms plateau) presented at a faster rate (200–400 ms). Latencies were corrected to account for the systematic 1.5-ms delay of the sound delivery system.

For both recordings, continuous signal contained no interictal epileptic activity. While supratemporal AEPs were referred to a...
contact located in the temporal bone, thalamic AEPs were bipolar (C1–C2) to optimize the MGB signal-to-noise. This choice was motivated by two considerations. First, as seen in Fig. 1d, auditory response on C2 was not reproducible across subaverages, and thus mainly reflected physiological noise. Second, using any other electrode as a reference (e.g. bone or C4) lead to less reproducible subaverages, meaning that C1 and C2 probed similar volume-conducted spurious activity.

**Independent subaverages and bootstrap averages**

To assess the reproducibility of the data we built independent subaverages (Figs 1d and 2b), by randomly splitting the initial set of N single trials into four subsets and building one average for each subset. The four subaverages, built from different trials, were statistically independent, allowing use of statistical tests on measures made on these curves. However, these subaverages were too noisy to precisely determine the latencies of the components.

Hence, we adapted the bootstrap approach introduced by Efron (1979) and usually used to estimate the probability density function of a statistical variable from a set of observed values. Here, for each stimulus, we constructed a distribution of 1000 bootstrap average responses, each of which was obtained by drawing with replacement N trials among the N initial trials, and averaging them. Latencies were measured on these averages, and histograms of the delays between thalamic and cortical components were constructed. Sharp histograms characterized stable delays across trials.

**Results**

**Description of the human MGB response**

In the first paradigm, the MGB response was most pronounced for the 250-Hz tone, lasting >300 ms with two initial sharp positive peaks at 21 and 29 ms, followed by two broader negativities at 50 and 200 ms (Fig. 2a). In the following, these components are termed P21, P29, N50 and N200, respectively. The same pattern was observed for frequencies up to 2000 Hz, although becoming overall weaker as frequency increased. Only P21 was detected for 4000 Hz. The P29 appeared as a clear peak only for 250 Hz, and as a shoulder on the descending slope of P21 for 500 and 1000 Hz. In the second paradigm, an earlier high-frequency negative peak was detected at 13.5 ms (N13) in addition to the already mentioned components (Fig. 3b). Its latency was determined at the local minimum preceding P21.

**Effect of tone frequency**

We found P21 amplitude (measured on four independent sub-averages) inversely proportional to the logarithm of the tone frequency (Fig. 2b, filled circles; $r^2 = 0.866, P < 0.0001$). Because we used SL sound levels, the five frequencies were presented at different sound pressure levels (SPL) intensities. This, however, could not explain amplitude variations of P21: 1000 and 2000 Hz tones had identical SPL intensities but P21 was smaller for 2000 Hz than for 1000 Hz (paired two-tailed t-test, $t_5 = 7.397, P = 0.0051$). Similar results (Fig. 2b, open circles) were obtained for N50, which could be consistently identified for frequencies of up to 2000 Hz ($r^2 = 0.638, P = 0.0002$). The broad N200 (150–350 ms) was clearly identified <1000 Hz, with no clear amplitude variation ($r^2 = 0.021, P = 0.65$), but higher latencies for lowest frequencies ($r^2 = 0.503, P = 0.0098$).

**Respective timing of thalamic and cortical activities**

We next determined the temporal relationship between early MGB and cortical components. We found the two earliest polarity reversals in medial Heschl’s gyri (probably stemming from different locations) at 23 ms between contacts H1 and H2/3 and at 27 ms between H1 and H2. Polarity reversals between neighbouring contacts are generally assumed to reflect local dipolar synaptic activities perpendicular to the cortical surface. Electrode H was indeed not parallel to the cortex (Fig. 1a), especially near the deepest contacts showing polarity reversals. We found that MGB P21 preceded by 2 ms the first cortical polarity reversal, and MGB P29 lagged by 1 or 2 ms the second one (Fig. 3a). In the second paradigm (Fig. 3b), the MGB N13 component was followed 3.5 ms later by a newly recorded cortical peak on contact H1 at 17 ms, which corresponded to one of the earliest human auditory cortical activities reported in the literature (Celesia, 1976; Liégeois-Chauvel et al., 1991). In this experiment, MGB P21 and P29 (detected as a distinct peak on 727 of the 1000 bootstrap averages) were also found to precede and lag, respectively, polarity reversals in auditory cortex by 1.5–2 ms (Fig. 3b).
Discussion

This descriptive study provides new functional data on the human MGB and on the respective timing of auditory thalamic and cortical activities.

The MGB response depended on stimulus frequency, with strongest P21 and N50 for lowest frequencies. These amplitude variations did not reflect a low-pass filtering behaviour of the MGB, because the amplitudes of the cortical components (for instance that just following the MGB P21 at 23 ms) were much stronger for 1.0 and 2.0 kHz than for other frequencies. In cats and monkeys, the MGB ventral division is known to be tonotopically organized with a low-to-high gradient of best frequencies running from lateral to medial (Aitkin & Webster, 1971; Gross et al., 1974; Imig & Morel, 1983). Our recording contact C1 lying lateral to the MGB, we suggest that the human MGB may also contain such a latero-medial tonotopically organized area, although tonotopy could not be proven with only one recording site.

Because the MGB has been poorly described in humans, and because animal literature (reporting complex MGB activity in awake animals: Allon et al., 1981; Meeren et al., 2001) is difficult to relate to human data, the classical interpretation of early human AEPs (brainstem and middle-latency components) remains simplified, with subcortical structures often viewed as simple relays of the ascending acoustical information only transiently activated at the earliest stage of auditory processing. We found here that the human MGB activity was in fact rather complex and long-lasting. Its temporal pattern actually strikingly resembled quasi-intracellular recordings of cat
ventral MGB units showing successive excitatory (at 8 and 15 ms) and inhibitory (at 50 and 200 ms) postsynaptic potentials following click stimulation (Etholm, 1976). MGB and cortical components appeared interlaced with latency intervals between 1.5 and 3.5 ms, compatible with primary thalamocortical delays of 1.2 and 1 ms in anaesthetized (Shaw, 1991) and freely moving (Meeren et al., 2001) rats, respectively.

We found earliest cortical activity at 17 ms, which is longer than published latencies as short as 8–12 ms in monkeys (Arezzo et al., 1975; Steinschneider et al., 1992) and 9–16 ms in humans (Celesia, 1976; Liégeois-Chauvel et al., 1991; Steinschneider et al., 1999). Longer latencies may first be attributed to the important intersubject variability of human initial cortical latency (Liégeois-Chauvel et al., 1991). They are indeed consistent with initial multunit latencies in medial Heschl’s gyrus of 15–25 ms (Howard et al., 1996). Alternatively, it is possible that an earliest cortical activity which we did not detect takes place. We indeed used tone stimuli, which do not elicit such strong early responses as do classically used abrupt-onset click stimuli. An earliest MGB activity would then be expected before 10 ms, which may possibly correspond to the subcortical activity presumably originating from the MGB) found with clicks at 8 ms by Hashimoto et al. (1981).

The intimate interlacing of thalamic and cortical activities suggest a close cooperation between MGB and cortex at the early stage of auditory processing, which may stem from early activation of several auditory thalamocortical and corticothalamic pathways (Morel & Imig, 1987; Pandya et al., 1994; Molinari et al., 1995), and further support a major role of the thalamus in sound perception.

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Abbreviations
AEPs, auditory evoked potentials; EEG, electroencephalography; LGB, lateral geniculate body; MGB, medial geniculate body; MRIs, magnetic resonance images; SPL, sound pressure level.

References