Mental chronometry of target detection: human thalamus leads cortex

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Attentive monitoring of environmental stimuli is most fundamental for rapid target detection. The aim of this study was to assess the timing of thalamic versus cortical processes involved in this cognitive operation. To this end, simultaneous depth and scalp EEG was recorded in eight patients with essential tremor, undergoing thalamic deep brain stimulation (DBS), when the DBS electrodes could be accessed via their temporarily externalized leads. The patients performed an oddball task consisting of 300 presentations of one frequent and two rare visual cues, appearing in randomized order. One of the rare cues was defined as a target, the occurrences of which had to be indicated by a button press (motor condition) or silently counted (non-motor condition). At the scalp and the thalamus, event-related potentials (ERP) were largest upon target presentation, with peak latencies in the time domain of classical P300 responses. Remarkably, target-specific thalamic ERP emerged significantly prior to scalp P300. Furthermore, whereas scalp ERP had a higher amplitude upon rare than upon frequent non-target signals, thalamic ERP were independent of stimulus probability. This pattern was identified during motor and non-motor task execution. We conclude that the human thalamus specifically supports the early recognition of target events and can widely distribute this label through its divergent cortical projections.

Keywords: thalamus; cortex; event-related potentials; cognition

Abbreviations: DBS = deep brain stimulation; ERP = event-related potentials; OT = oddball task; VIM = ventral intermediate nucleus


Introduction

A frequent observation in clinical neurology is that damage of the human thalamus can go along with symptoms primarily assigned to the human cortex, such as anosognosia and aphasia (Katz et al., 1987; Starkstein et al., 1992; Crosson, 1999). In this context, the recent proposal of a thalamic support function for speedy cognition is intriguing (Van Der Werf et al., 2001) as it predicts a general role of the human thalamus in higher order mental processes.

A fundamental cognitive operation, facilitating the rapid selection of relevant information, is the attentive monitoring of environmental stimuli. Such behaviour can be chronometrically described by event-related potentials (ERP) in conventional scalp EEG, particularly by the parietal ‘P300’ response: this ERP component reflects the intentionally ascribed importance and salience of a sensory event and peaks 300–600 ms after stimulus presentation at posterior scalp sites as a positive potential (Sutton et al., 1965; Johnson and Donchin, 1978; Polich, 1990). Its origin is attributed to both cortical (Verleger et al., 1994; He et al., 2001; Goldstein et al., 2002) and subcortical areas (Yingling and Hosobuchi, 1984; Katayama et al., 1985; Velasco et al., 1986; Kropotov and Etlinger, 1991; Rektor et al., 2001).

Naturally, invasive recordings in humans are rare. However, in selected patients, e.g. undergoing deep brain stimulation (DBS) as treatment for movement disorders, extended intrathalamic EEG can be derived from transiently externalized depth-electrodes simultaneously with additional scalp EEG (cf. Marsden et al., 2000; Foffani et al., 2003; Kuhn et al., 2004). Over the last decade, DBS has been established as a therapy for the treatment of disabling movement...
disorders, specifically in Parkinson’s disease, primary dystonia or severe tremor conditions, once they do not respond or have become refractory to drug treatment (Benabid et al., 1998; Krack et al., 1998; Schuurman et al., 2000). In DBS, high frequency electrical impulses act as a modulatory factor on the aberrant function of specific motor nuclei within the basal ganglia or the thalamus. The discharges are delivered from a programmable subcutaneous battery connected to the depth electrodes, which, in case of tremor, are commonly inserted in the thalamic ventral intermediate nucleus (VIM), where symptoms can often be completely suppressed (Schuurman et al., 2000).

To elucidate the temporal relation between thalamic and cortical activations during target selection, eight patients with bilateral thalamic DBS implants for tremor therapy performed a classical visual oddball task (OT) for eliciting P300 responses while intrathalamic and scalp ERP were recorded simultaneously.

Subjects and methods

Subjects

Eight cognitively unimpaired patients (two females, six males; 36–73 years; Mini-Mental State: 28.6 ± 1.4 out of 30 points, range 26–30, cut-off for suspected dementia ≤23; cf. Fillenbaum et al., 1990) with essential tremor, undergoing DBS of the thalamic VIM, performed an OT during the simultaneous recording of intrathalamic and scalp EEG. Recordings were performed during the first days after DBS-electrode placement with leads externalized to assess the clinical efficacy of electrode localization and to confirm it by MRI (normal pre-surgical MRI scans in all patients), before the definite DBS-stimulator was implanted in a second operation. Owing to the short-lived post-operative micro-thalamotomy effect (cf. Kondziolka and Lee, 2004), patients were almost tremor-free at this moment. Global tremor severity (cf. Fahn et al., 1993) was rated on a scale from 0 to 4 (0 = absent; 1 = mild, intermittent; 2 = moderate; 3 = markedly abnormal, interfering with many activities; 4 = severely abnormal, interfering with most activities). Pre-surgical tremor severity of the patients was rated 2.9 ± 0.5, the post-surgical value being 0.7 ± 0.7 at a minimum of 6 months follow-up. All patients gave informed consent to the study protocol, approved by the Ethics Committee of the Charité Campus Benjamin Franklin.

Oddball task

Three hundred visual stimuli were presented per session with interstimulus intervals of 2 s. The symbols appeared for 150 ms within a quadratic frame of 6 × 6 cm² in the middle of a 15 inch computer screen with the patient sitting at a distance of 1.5 m. An x-like stimulus (14% probability of occurrence) was defined as target upon which a right index finger button press had to be carried out as accurately and rapidly as possible (Fig. 1). Non-targets were either equally rare (14% z-like shape) or frequent (72%, cross). Each stimulus class and the button press responses were encoded by distinct trigger signals stamped onto the continuous EEG-file.

Control experiments

First, to discriminate lateralized motor effects, four out of eight VIM-patients performed the task twice, responding with either the right or the left index finger.

Secondly, in four additional subjects, DBS recordings were performed under the (non-motor) instruction to silently count the number of OT targets.

Thalamic recordings

Electrodes were implanted bilaterally into the VIM (Medtronic® electrode 3387). For electrode placement, standard VIM positions from the stereotactic brain atlas by Schaltenbrand and Wahren (1977) were referred to the individual AC-PC line (the straight sagittal connection between anterior and posterior commissure), exactly identified by intraoperative ventriculography. Standard coordinates were adjusted for each case with respect to the individual thalamic height (15.3 ± 1 mm) and AC-PC length (24.8 ± 1.5 mm), determined by matching pre-surgical stereotactic MRI with ventriculographic data. Thus, calculated coordinates for the lowest contact of the right/left DBS electrode, expressed as (i) anteriority to PC, (ii) laterality to AC-PC and (iii) verticality to AC-PC, were as follows: (i) 7.2 ± 0.4 mm/7.5 ± 0.5 mm, (ii) 14.6 ± 0.5 mm/14.5 ± 0.5 mm and (iii) −0.1 ± 0.4 mm/−0.2 ± 0.6 mm (minus, indicating below AC-PC). Post-surgical MRI confirmed that the planned placements were met by the implanted electrodes.

Two bipolar channels were recorded per DBS-electrode, i.e. four channels per patient. The implants consist of four ring contacts (contacts 0–3) of 1.5 mm width, longitudinally spaced at distances of 1.5 mm in VIM implants. On both recording sides the most basal and its neighbouring contact (0/1) were referenced to the most cranial contact (3), resulting in bipolar derivations of 4.5/7.5 mm width, respectively.

Surface recordings

Twenty scalp electrodes (Neuroscan system) were positioned according to the 10–20 system (Fz, F3, F7, F4, F8, FCz, FC3, FC4, Cz, C3, C4, CP1, CP3, CP2, CP4, Pz, P3, P4, O1 and O2; impedances < 5 kΩ), referenced to linked mastoid electrodes. The multi-electrode array was used to verify intra-individually the typical spatiotemporal pattern of P300 scalp responses, which could be identified in all but one patient with maxima consistently at Pz. Accordingly, P300 amplitudes and latencies at Pz were used for further analysis. In four VIM-implanted patients, bipolar dorsopalmar EMG-recordings from the spatium interosseum II of the active hand were performed in order to assess the onset of finger movements in target trials. Thalamic and scalp data were sampled continuously at 2 kHz with a bandpass from 0.05 to 500 Hz. Horizontal and vertical EOGs were registered to screen against eye blink artefacts.
Analysis

Peristimulus EEG-segments from −1 to +1.5 s were averaged selectively for all stimulus classes. For target trials, averages were additionally calculated relative to the button presses. Thus, back-averages from the motor response could be compared with conventional stimulus-triggered forward-averages. Trials with eye movement or blink artefacts were excluded from further analysis. Only 44 (out of 2400 trials presented over all patients) were erroneous (target omissions or responses to non-targets) and were therefore dropped, leaving only correct trials for further analysis. Scalp and thalamic EEG responses were filtered off-line from 0.5 to 20 Hz.

The component peak values were determined relative to a 1 s pre-stimulus baseline in case of monophasic potentials, as regularly observed for P300 components at parietal scalp sites. In the sequence of components recorded from frontal electrodes, the first deflection was measured baseline-to-peak and subsequent potentials peak-to-peak. ERP from the main experiment were analysed using planned two-sided paired $t$-tests with Bonferroni corrections for Pz, Fz and thalamic derivations. Results were considered as significant at $P < 0.05$.

Results

Overview

The patients detected targets almost flawlessly (error rate <2%) with a mean reaction time of 452 ± 96 ms. Oddball scalp ERP showed a typical distribution over frontal, central
and parietal recording sites (Fig. 2): the recordings contained the well-known P300 mid-parietal voltage maxima upon target stimuli (Figs 2 and 3A) with peak latencies ~490 ms. In contrast, simultaneous thalamic recordings revealed target ERP peaking already at 340 ms (Figs 2 and 3B).

**Amplitude analysis**

In an initial exploratory analysis (Bonferroni corrections omitted for maximizing sensitivity), recordings from all scalp electrodes had been subjected to *t*-tests, searching for significant differences between target and non-target...
Early thalamic target detection

Brain (2006), 129, 923–931

responses as well as between frequent and rare non-target responses: Only parietal, and to a lesser degree central scalp electrodes showed significant peak amplitude differences. The peak latencies of these components were found in the P300 domain at ~490 ms and coincided in parietal and central electrodes. Concerning scalp ERP peaks prior to this typical parietal P300, a positive potential peaked ~160 ms over mid-frontal sites in five out of eight patients, previously labelled as frontal ‘P2’ (Oades et al., 1995), followed by a negative and subsequent positive deflection ~230 ms (‘N2’) and 380 ms (‘P3a’), respectively. Notably, frontally no significant differences between responses to the distinct stimulus classes were found. Nonetheless, we retained Fz for further analyses, in particular for latency comparisons between scalp and thalamic ERP, because additional cognitive components have been described previously in frontal scalp recordings (e.g. P3a/novelty-P3; cf. Courchesne et al., 1975; Squires et al., 1975; Friedman et al., 2001; Simons et al., 2001; Barceló et al., 2002; Debener et al., 2002, 2005).

Thus, for the final analysis we referred to those frontal and centroparietal recordings displaying the largest P300-amplitudes (Pz, Fz), according to recommended measurement strategies of oddball-ERP (Fabiani et al., 1987; Polich, 1988), and additionally included the intrathalamic recordings available in the present study. The statistical results from these analyses were Bonferroni-corrected.

We found that the amplitude differences between target versus rare/frequent non-target responses were significant at Pz and the thalamic level (Pz: \( P = 0.003/0.04 \); thalamus: \( P = 5.2 \times 10^{-10}/7.5 \times 10^{-10} \); Fz: n.s.).

A first major distinction between intrathalamic and parietal scalp ERP became apparent in the processing of non-target stimuli (Fig. 3A and B) as graded response amplitudes to non-targets were observed in surface records only: mid-parietal scalp ERP were significantly smaller after frequent (72%) non-targets than after rare (14%) non-targets \((P = 0.002)\) whereas intrathalamic ERP to non-targets of either probability showed almost identical amplitudes (difference n.s.).

Amplitude values are summarized in Table 1, relevant statistical findings in Fig. 7. Thalamic data are provided for the wide derivation (contact 0–3, 7.5 mm width). The narrower derivation (contacts 1–3, 4.5 mm width) yielded qualitatively identical results (amplitudes 61% for frequent non-targets, 60% for rare non-targets and 64% for targets of those obtained by the wide intrathalamic derivation; latencies identical).

### Latency analysis

The peak latency difference between parietal P300 (490 ms) and intrathalamic target responses (340 ms) was highly significant \((P = 1.6 \times 10^{-5})\); ERP difference curves (‘target minus rare non-target’) demonstrated that thalamic target ERP preceded the parietal P300 response in scalp recordings (Fig. 3C).

As discussed above, no significant target-related ERP could be detected outside the centroparietal area. In the motor condition, a subgroup of five patients showed deflections at Fz with peak latencies earlier than the parietal P300. In an intraindividual peak latency comparison of these frontal P3a-like components versus thalamic target components, the latter consistently \((n = 5)\) preceded the frontal P3a-like component, on average by 66 ms.

### Control experiments

In the four patients with right-hand and left-hand task performances, surface EMG records of both hands (eight sessions) revealed that thalamic target responses peaked \(69 \pm 23\) ms prior to movement-onset. Further, it could be shown \((i)\) that amplitudes and latencies of target responses were accurately reproduced, no matter if reactions were carried out with the right or left finger [despite reaction times on average 56 ms slower for left-hand side than right-hand side performance (Fig. 4)] and \((ii)\) that intrathalamic target ERP are unrelated to motor performance as thalamic target responses were larger than non-target ERP also when patients silently counted targets (Fig. 5A). This result is further corroborated by averaging target ERP backwards from the button press. Here, amplitudes were found attenuated in comparison with the standard forward average triggered by the stimulus, indicating a tighter time relation of the ERP to stimulus processing than to the preparation of the motor response (Fig. 5B). In a similar comparison of backward-averaged and forward-averaged target ERP,

### Table 1 P300 amplitudes and peak latencies

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Thalamus</th>
<th>Scalp: Pz</th>
<th>Scalp: Fz</th>
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<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>P300b</td>
</tr>
<tr>
<td>OT: ERP peak latencies (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-targets (72%)</td>
<td>245 ± 16</td>
<td>241 ± 21</td>
<td>468 ± 110</td>
</tr>
<tr>
<td>Non-targets (14%)</td>
<td>249 ± 17</td>
<td>241 ± 23</td>
<td>486 ± 116</td>
</tr>
<tr>
<td>Targets (14%)</td>
<td>345 ± 66</td>
<td>342 ± 52</td>
<td>494 ± 98</td>
</tr>
<tr>
<td>OT: ERP amplitudes (μV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-targets (72%)</td>
<td>4.4 ± 3</td>
<td>4.6 ± 3.2</td>
<td>4.3 ± 2.5</td>
</tr>
<tr>
<td>Non-targets (14%)</td>
<td>4.5 ± 3</td>
<td>4.6 ± 3.1</td>
<td>7.4 ± 3.1</td>
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<tr>
<td>Targets (14%)</td>
<td>13.7 ± 7.6</td>
<td>13.1 ± 7.2</td>
<td>13 ± 6.3</td>
</tr>
</tbody>
</table>

Mean peak-latencies (±SD) and amplitudes (±SD) of the intrathalaminically recorded responses and scalp potentials (electrodes Fz/Pz).

In italics: positions, from which target-specific activity was recorded.
a motor-related contribution in the P3a time domain became evident at frontal scalp recording sites (Fig. 6), which might contribute to the minor (and non-significant) difference between target and rare non-target ERP around P3a latency. In the non-motor condition, frontal N2 and P3a-like components could not be identified, and in ‘target minus non-target’ difference curves no significant target-related frontal activity in the time domain of P2, N2 and P3a could be delineated, whereas the simultaneously recorded intrathalamic ERP showed a distinct target-related component comparable with the motor condition, i.e., the early thalamic target component was observed independent of the presence or absence of frontal P3a-like scalp ERP components.
Discussion
Cognitive thalamic ERP were consistently identified together with classical P300 scalp ERP. The time course of these responses provides significant information on the rapidly changing system states during a task requiring the selective recognition of visual stimuli. P300-like components in depth-recordings have been described previously (Yingling and Hosobuchi, 1984; Katayama et al., 1985; Velasco et al., 1986; Kropotov and Etlinger, 1991; Kropotov and Ponomarev, 1991; Rektor et al., 2001), but intraindividual chronometric ERP comparisons between thalamic and cortical activation patterns have not been available so far.

Scalp P300 components primarily mirror cortical activity. The target-specific parietal ‘P3b component is supposed to arise from temporoparietal and cingulate areas (Verleger et al., 1994; Soltani and Knight, 2000; He et al., 2001; Goldstein et al., 2002; Dien et al., 2003). Generators around the temporoparietal junction and in the anterior cingulum were also found to contribute to the novelty-related P3a response, in addition to prefrontal lateral and orbitofrontal cortical sources (Baudena et al., 1995; Ranganath and Paller, 1999; Brazdil et al., 1999; Clark et al., 2000; Bledowski et al., 2004).

Concerning ERP recorded in VIM, a couple of arguments favour an intrathalamic generation. First, the latency discrepancy between potentials from scalp versus thalamus is not compatible with a cortical activation, which—through volume conduction—would show up also at the thalamic level. On the contrary, the asynchronous time courses of components detected from depth and scalp electrodes along with the magnitudes of thalamic ERP, which were large despite bipolar derivations of few millimetres width only, support a local generation of the depth signals. Concurrently, Kropotov and Ponomarev (1991) reported on P3-like components in the sensorimotor thalamus peaking ~360 ms, and demonstrated that these ERP were accompanied by a significant increase of neuronal activity in VIM proper. Furthermore, the sensorimotor thalamus was hypothesized to work as a monitoring system of different informational streams for motor decision making (Guillery and Sherman, 2002a, b), integrating ongoing motor and cognitive requirements. Finally, based on diverse experimental findings, focal attention, arousal and target selection functions were ascribed to thalamic areas such as the centromedian nuclei and the pulvinar (Posner, 1987; Coull et al., 1997; Portas et al., 1998; Sarter et al., 2001; Woldorff et al., 2004). Thus, although the exact origin of VIM-recorded ERP remains open in clinical cases with just one electrode trajectory being available, their thalamic generation can be regarded as highly probable.

Specifically, deep brain recordings reveal two distinguishing features of thalamic and cortical processing, one concerning amplitude patterns of non-target ERP, the other timing differences of target components. First, whereas the parietal ERP were sensitive to non-target probabilities, the thalamic activations were found identical upon non-target stimuli of different probabilities and, thus, are compatible with context-independent, stimulus-driven arousal bouts in brainstem-thalamocortical pathways (Woldorff et al., 2004). Interestingly, it has been demonstrated that the mid-brain reticular formation has dense synaptic connections with intralaminar thalamic areas, such as the centre median and centrolateral nuclei, which themselves project widely to multiple cortical areas (Bentivoglio et al., 1981; Steriade and Glenn, 1982; Macchi et al., 1984; Jones, 1998; McFarland and Haber, 2002). Besides controlling vigilance, e.g. maintaining alert states or governing sleep-wake transitions (Moruzzi, 1972; Glenn and Steriade, 1982; Steriade et al., 1982), this system is activated during attention-demanding visual and auditory tasks, suggesting an anatomical route for the maintenance or amplification of stimulus-related arousal, with the thalamus linking the mid-brain to the cortex (Kinomura et al., 1996). In contrast to such stimulus-driven alerting, the specific representation of stimulus probabilities in scalp non-target ERP indicates additional cortical processing, modelling the occurrence frequency of environmental conditions (Johnson and Donchin, 1978; Polich, 1990).

Notably, the observed target selectivity of thalamic activity goes beyond an unspecific arousal bout and implies an additional knowledge-driven process. The thalamus might be informed about sensory target features through priming of thalamic reactivity by cortical sensory templates, tonically provided throughout the task, e.g. by corticothalamic projections: a convergence of sensory bottom-up signals and sustained attentive top-down control was proposed to occur in thalamic areas, such as the centre median and parafascicular nuclei (Sarter et al., 2001; Woldorff et al., 2004). A mechanism for this interaction could be the capability of corticothalamic projection neurons to sharply synchronize neuronal activity of thalamocortical cells (Funke et al., 1996; Worgotter et al., 1998), thus improving synaptic transmission at their respective projections (cf. Lisman, 1997).

Secondly, thalamic target-related ERP peaked clearly prior to the parietal scalp P300 (340 versus 490 ms). As this finding might have profound implications for the ubiquitous use of P300 as timing mark of cognitive processing, the question arises whether scalp ERP prior to parietal P300 were observed, potentially coinciding with or even preceding the thalamic target ERP. Whereas the initial group analysis had revealed no significant target-specific activity outside the centroparietal area, a frontal component preceding the parietal P300 was identified individually in a subset of five out of eight patients, showing some spatiotemporal characteristics of P3a (Friedman et al., 2001; Barceló et al., 2002). The important finding in the present context of combined scalp and intrathalamic records is that both, the parietal P300 and the frontal P3a-like component peaked later than the thalamic target ERP. As to the amplitude analysis, no statistically significant frontal amplitude differences between target and non-target ERP were found so that this component differs from thalamic ERP also functionally. Furthermore,
the independence of thalamic and frontal scalp ERP is corroborated by the additional finding that distinct intrathalamic target-related activity was recorded also in the non-motor (silent-counting) condition when no frontal scalp ERP components were identifiable.

Taken together, the latency differences differentiate thalamic from scalp-derived ERP as discrete target-specific components. Notwithstanding, their shared target specificity permits a chronometry of cognitive operations where thalamic and cortical activations can be viewed as complementary: early thalamic event-related activity reflects the momentary relevance of a stimulus as behavioural target and can widely distribute this label through its divergent cortical projections. Following this basic stimulus labelling, cortical processing integrates a refined analysis of non-sensory context-dependent stimulus attributes, such as probability of recent occurrences.

Two conceptual consequences for studies on human cognition follow from the present results: First, the observed thalamocortical latency differences of target ERP call for a conservative interpretation of the timing and onset of cerebral cognitive processes when based on standard scalp ERP. Secondly, the early cortical involvement in target processing underpins the recently proposed role of the thalamus for cognitive speed (Van Der Werf et al., 2001) on a neurophysiological basis.

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Early thalamic target detection

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