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Ageing-related changes in the processing of attended and unattended standard stimuli

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RESPONSES to standard stimuli presented during a dichotic listening task were analysed in 53 healthy subjects from 20 to 86 years of age. The aim was to determine whether N1 and P2 waves showed changes attributable to attention or more general changes underlying the electrophysiological processing of such stimuli under attended and unattended conditions. N1 was larger at midline frontal and central electrodes in middle-aged and in elderly subjects without changes in its topographical distribution. These changes were independent of attention. P2, which was also larger in middle-aged and in elderlies, showed scalp distribution changes depending on the direction of attention. The present results indicate the existence of general ageing-related changes in the processing of attended and unattended standard stimuli which may be related to inhibitory deficits (N1) and to changes in the orientation of electrical sources (P2). *NeuroReport* 10:2383–2388

Key words: Ageing; Attention; N1; P2; Unattention

Introduction

In auditory oddball tasks in which target stimuli require the focusing of attention by the subject, standard stimuli reliably elicit two waves, N1 and P2. The amplitude of these waves has previously been found to be significantly larger in middle-aged and in elderly persons [1,2] executing an oddball task with mental counting. The interpretation of such results has been the existence of a progressive deficit with increasing age in the capacity to withdraw attentional resources from stimuli which require only marginal attention [1].

Whether the increase of N1 and P2 amplitudes with ageing is due to an attentional deficit or to a more general ageing-related change in the electrophysiological processing is difficult to determine with an active oddball task because when the subject is executing the task some degree of attention is required by the standard stimuli to be rejected from the decision process (i.e. mental count or button press to the appearance of each target stimulus).

In sensory auditory and visual event-related potentials (ERPs) which are obtained in passive, attention-independent conditions, a consistent finding has been an ageing-related enhancement of amplitudes [3–5]; this has been interpreted as an index of a decrease in the inhibition of the activity related to the elicitation of these ERPs.

One way to test the role of attentional processes on the age-related changes in N1 and P2 amplitudes is to study these waves under unattention and attention conditions. In this study, N1 and P2 were recorded during a dichotic listening task in healthy subjects ranging in age between 20 and 86 years with the aim of determining ageing-related changes in the electrophysiological processing of the same standard stimuli when attended and when ignored. If ageing-related changes in the amplitudes of these waves depend on the abnormal maintenance of attentional resources on standard stimulation, then no significant changes are expected in the responses to these stimuli when unattended.

In previous studies no age-related changes have been found in N1 and P2 obtained with a dichotic listening task in samples including young, middle-aged and elderly subjects [6,7]. However, since differences between young and elderly subjects have recently been observed in these waves recorded during active oddball tasks with larger samples [1,2], we would expect at least the same results observed in the attended conditions of selective attention tasks.

Materials and Methods

Subjects: Fourteen young (five females, age 31 ± 6 years, range 22–39), 14 middle-aged (seven females, age 50 ± 7 years, range 41–59) and 25 elderly subjects (17 females, age 72 ± 6 years, range 61–86) were tested. Subjects were recruited from volunteers having participated in previous studies in this laboratory. Subjects were equal in years of formal education (young, mean 10 ± 5; middle-aged, mean

9 ± 4; elderly, mean 9 ± 5). None had experience with psychophysiological testing. The general exclusion criteria were diseases of the central and peripheral nervous system, cardiovascular diseases and/or hypertension, alcohol abuse, pulmonary problems, cranioencephalic trauma, audiological problems, and MEC scores lower than 28 (MEC = Mini Examen Cognoscitivo [8], the Spanish version of the Mini Mental State Examination [9]).

Stimuli and procedure: Pure sine-wave tones of 50 ms (10 ms rise and fall times) were generated by the Stim module of a Neuro Scan system and presented dichotically at an intensity of 90 dB SPL through TDH-39 headphones, with a constant ISI (offset-to-onset) of 600 ms. Standard tones had a frequency of 1000 Hz and were randomly replaced by deviant tones of 1500 Hz (probability of 0.2) with the restriction that there was at least one standard tone between two deviant tones. Two blocks of 400 tones (200 in each ear) were presented in two consecutive runs. In each run, subjects were instructed to pay attention to tones in the right or left ear and to press a button with the preferred thumb when they detected deviant tones in the attended ear while ignoring the stimulation in the other ear. The assignation of each ear as attended was counterbalanced across subjects. Two practice blocks of 60 tones (30 in each ear, six deviants) were given to the subjects to ensure a good level of performance. During the recordings, subjects fixated on a spot 2 cm in diameter fixed on the wall 150 cm from their eyes and were instructed to avoid movement and blinking.

The EEG (bandpass 0.1–30 Hz) was continuously amplified and digitized with the Scan module connected to a Grass Model 12 neurodata acquisition system at a rate of 256 Hz/channel, from 20 tin scalp electrodes inserted in a cap (Electrocap, Inc.) according to the 10-20 international system (Fig. 1). The active electrodes were referred to linked earlobes and grounded with an electrode placed between Fz and Fpz locations. Vertical and horizontal EOG activities were recorded bipolarly from above and below the left eye and from the outer canthi of both eyes, respectively.

For each electrode, EEG epochs consisting of 500 ms post-stimulus and 100 ms prestimulus were obtained off-line and averaged for the standard tones in each ear when attended and when non-attended, yielding a total of four averages in each subject. Trials exceeding $\pm 100\,\mu V$ were automatically excluded from the averages, as well as trials containing excessive eye movements or blinking.

Data analysis: The peak amplitudes and latencies of N1 and P2 were automatically measured relative to the 100 ms baseline at each of the 20 electrodes separately employing latency windows of 60–150 and 150–280 ms, respectively. The latency windows were adapted considering the intervals between which each wave appeared in the corresponding grand mean waveforms of each age group.

The values of N1 and P2 peak amplitudes were normalized [10] and subjected to mixed model analyses of variance (ANOVAs) in which age (young, middle-aged, elderly) was entered as the between-subjects factor. Ear (left, right), attention (attended-unattended), lateralization (left, right hemisphere), lateralized fronto-central electrode (one frontopolar, two frontal, one central), and midline electrodes (Fz, Cz, Pz, Oz) were used as within-subject factors. Whenever appropriate, degrees of freedom were corrected by the conservative Greenhouse-Geisser estimate. The peak latencies of N1 and P2 at Cz were subjected to mixed model ANOVAs with age group as between-subjects factor, and ear and attention as within-subject factors.

For scalp distribution analyses, a common average reference was calculated by averaging the data, time point by time point, across all 20 electrodes in each subject. Maps were computed using brain electromagnetic source analysis (BESA22) [11]. Scalp potentials rereferenced to the common average, excluding the EOG electrodes, were interpolated for mapping using the surface spline method. The current source density (CSD) maps were computed with the spherical spline interpolated data. The maps were computed at a single time point where N1 and P2 were largest in the grand mean waveforms of each age group.

Results

N1: In all subjects, N1 amplitude was larger over the hemisphere contralateral to the stimuli in the attended channels ($F(1,50) = 34.6$, $p \leq 0.0001$). In the two ears, when attended and when unattended, N1 peak amplitudes were larger at midline frontal and central electrodes in middle-aged and elderly subjects (age $\times$ midline electrodes, $F(6,150) = 3.5$, $p \leq 0.03$, $\varepsilon = 0.47$) than in young subjects (Figs 1,2). N1 peak latency was similar among age groups and remained unchanged across attended and unattended conditions.

The topographical distribution of N1 did not change with age, showing a distribution slightly ipsilateral to the unattended ear and contralateral to the attended ear in all subjects.

P2: P2 amplitude was decreased in all subjects at midline frontal and central electrodes when standard stimuli arrived through the attended ear (atten-

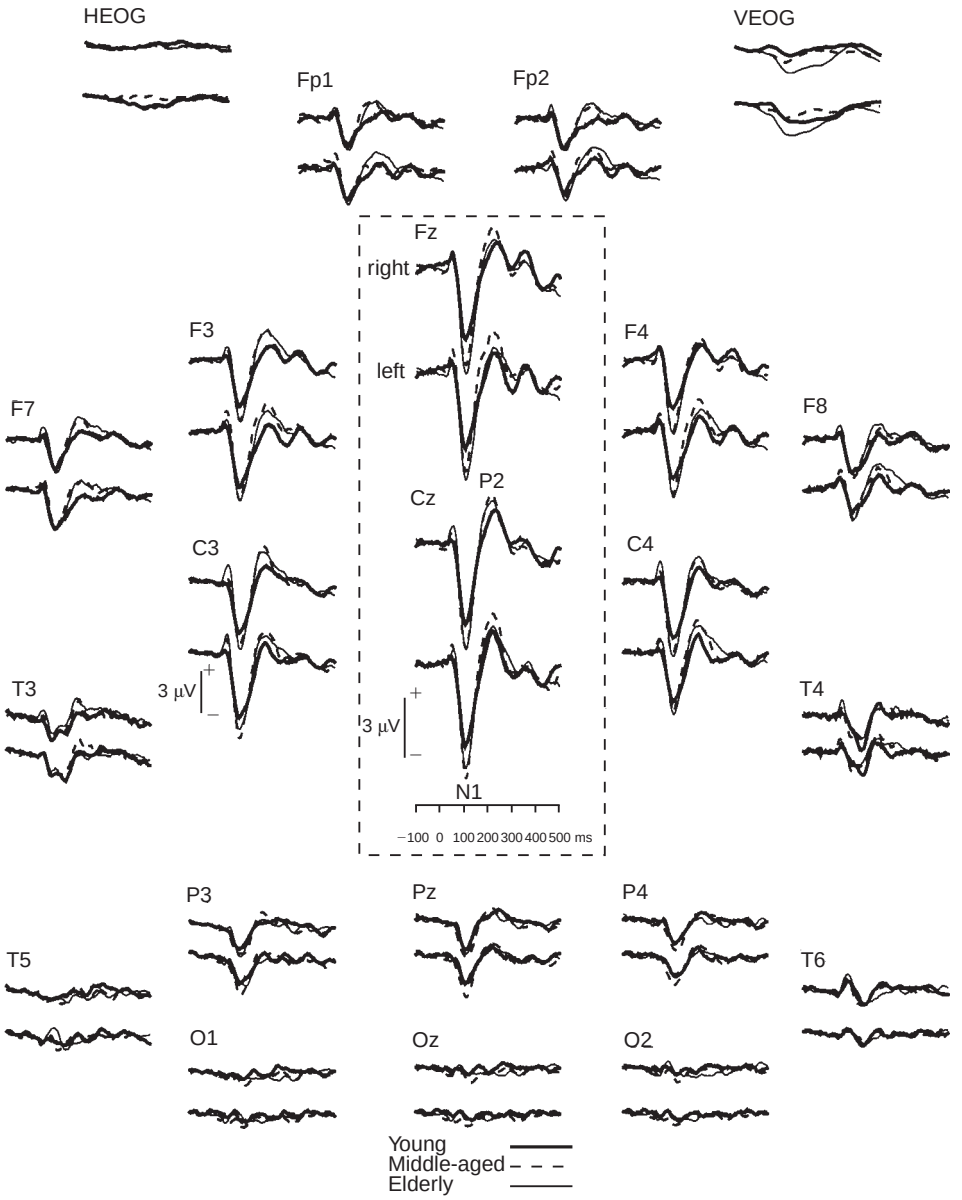

FIG. 1. Grand-mean ERPs showing N1 and P2 elicited to stimulation in the two ears under unattention conditions. At each electrode the upper waveforms correspond to the superimposed ERPs of each age group obtained to the stimulation in the right ear, and the lower ones those obtained to the left ear. Amplitudes at midline frontal and central electrodes have been enlarged by 40% of the amplitude at the other electrodes.

tion × midline electrodes, $F(2,50) = 9.6$, $p \leq 0.01$). P2 amplitudes were larger in middle-aged and in elderly subjects at lateral electrodes to attended and unattended stimuli (age × lateralization, $F(2,50) = 3.9$, $p \leq 0.03$). P2 latency failed to show ageing-related or attention-related changes.

In young subjects P2 showed a central distribution irrespective of the attended ear (Fig. 3). In middle-aged, and more markedly in elderly subjects, P2 was ipsilateral to the attended ear (Fig. 3). This enhancement of P2 amplitude over the hemisphere ipsilateral to the attended ear led to a reduction in elderly subjects of the attention-related differences observed in the amplitude of P2 (age × attention × lateralization, $F(2,50) = 4.9$, $p \leq 0.02$) for young and middle-aged subjects at frontal and central electrodes ipsilateral to the attended ear (Fig. 4).

Discussion

Ageing affected differentially N1 and P2 amplitudes in both attention and unattention conditions. In middle-aged and elderly subjects N1 presented larger amplitudes at midline frontal and central electrodes while P2 amplitude was enhanced at lateral electrodes. Moreover, N1 did not change its topo-

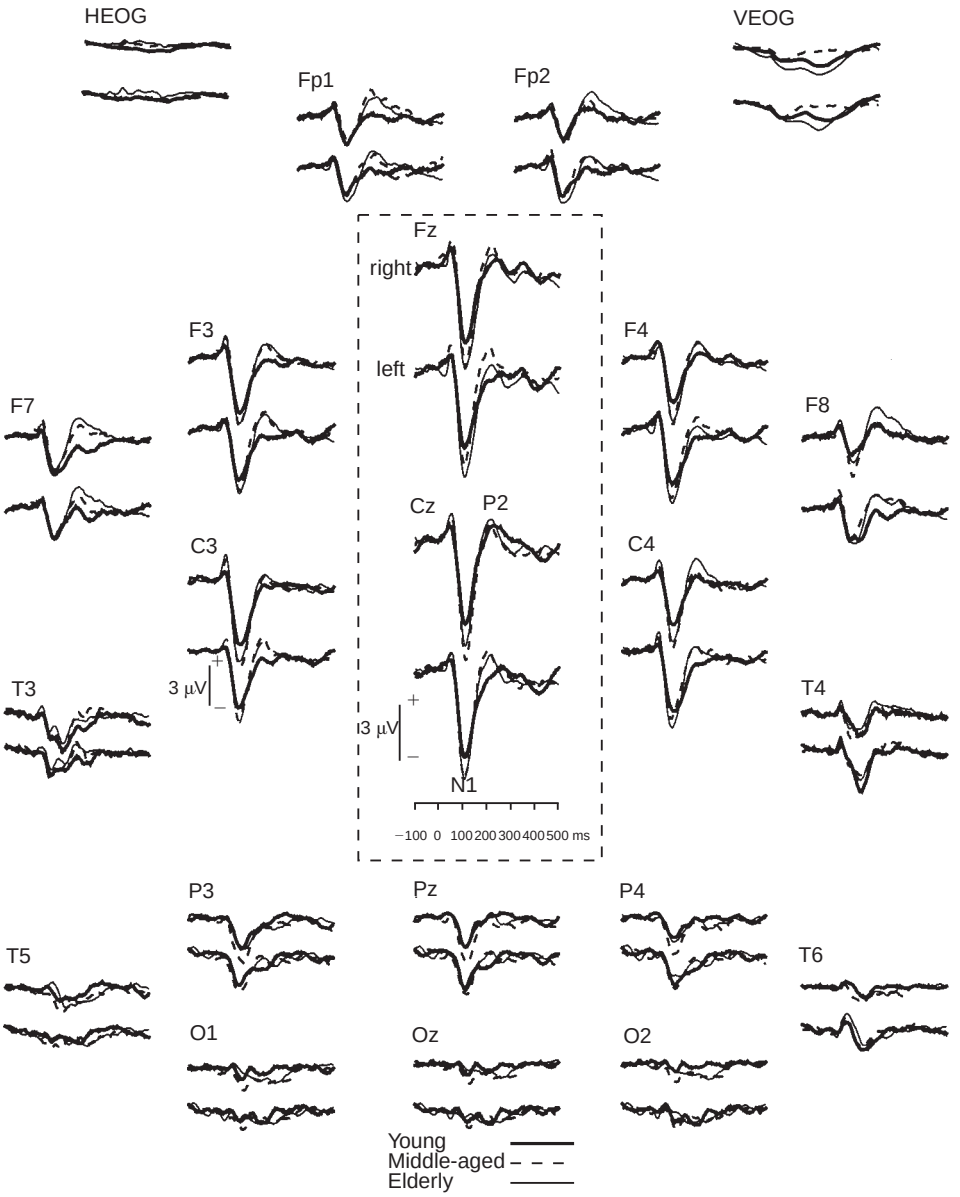

FIG. 2. Grand-mean ERPs showing N1 and P2 elicited to stimulation in the two ears under attention conditions. At each electrode the upper waveforms correspond to the superimposed ERPs of each age group obtained to the stimulation in the right ear, and the lower ones those obtained to the left ear. Amplitudes at midline frontal and central electrodes have been enlarged by 40% of the amplitude at the other electrodes.

graphical distribution with age, while P2 shifted to a more lateralized distribution with age which was ipsilateral to the attended ear.

The attention effects on N1 and P2 have previously been analyzed in young, middle-aged and elderly subjects, but no effects of age were found [6,7]. Ford and co-workers [6] analyzed only the N1 response at the vertex in all subjects and this may have limited their results. Woods [7] included in the middle-aged group subjects from 26 to 53 years of age, and this group represents a wide age range. Using such a wide age range may have led to the absence of differences between the two age groups.

Larger N1 amplitudes have been reported in subjects with frontal lessions [12] and in 4- to 6-year-old children compared with 6- to 8-year-old children [13]. These results have been interpreted as reflecting supression of frontal inhibitory influences on the generation of the N1 wave due to loss of frontal cortical tissue [12] and to incomplete frontal myelination [13]. Among the several changes that the aged human frontal lobes experience are a shrinkage of large neurons and of horizontal dendrites which are thought to have inhibitory properties (reviewed in [14]). Moreover, the loss of myelin in frontal lobes is one of the most characteristic

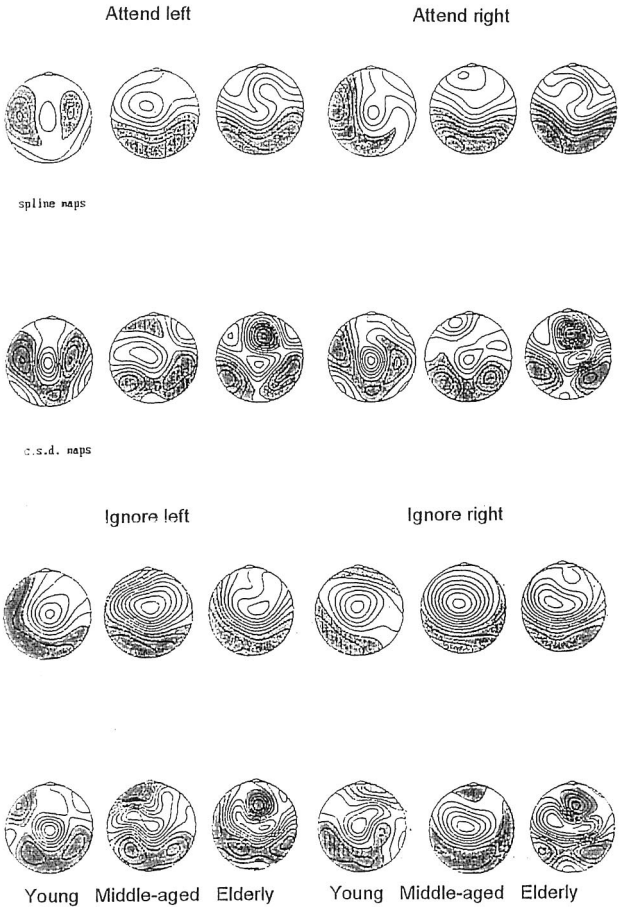

FIG. 3. Spline (rows 1 and 3) and CSD (rows 2 and 4) maps for P2 across age groups at each ear when attended and when unattended. In spline maps, isopotential lines are separated by 0.1 μV, in CSD maps they are separated by 0.05 μV/cm^2. Shaded areas indicate negative values (sinks for CSD maps), and unshaded areas indicate positive values (sources for CSD maps).

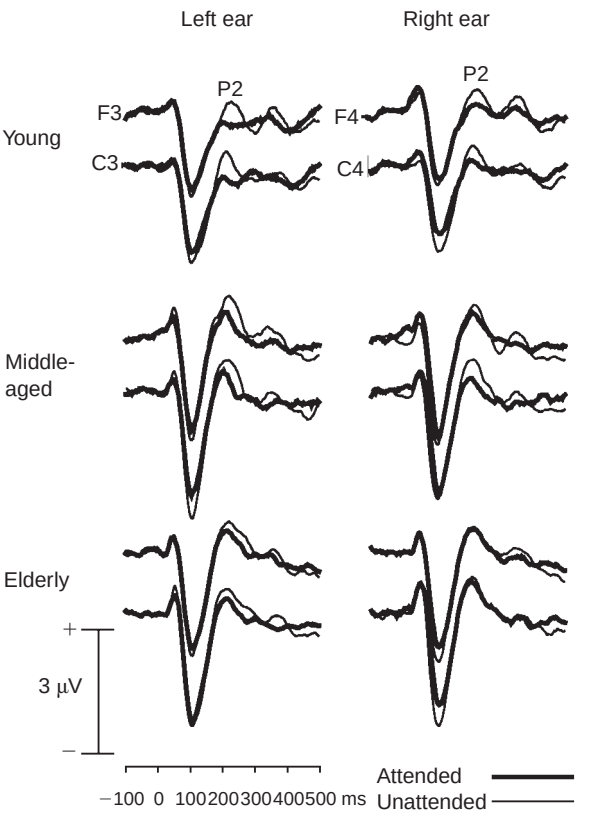

FIG. 4. Grand-mean ERPs of each age group showing P2 elicited to unattended and to attended stimulation at main frontal and central electrodes ipsilateral to the attended ear.

changes which happen in the aged brain (reviewed in [15]). It has been suggested that myelinated axons propagate impulses not only more rapidly but also with less energy and are less susceptible to abnormal transmission from fiber to fiber than unmyelinated axons (reviewed in [14]). Given that frontal and prefrontal cortices exert suppression of activity over multiple subcortical and cortical regions, the existence of the above ageing-related changes suggests that inhibitory deficits may underlie the increase of N1 amplitude observed in this report.

The effects of age on P2 amplitude were significant at lateral electrodes under attention and unattention conditions, and mainly at frontal and central electrodes ipsilateral to the attended ear, which led to a reduction in elderlies of the attention-related difference in P2 amplitude observed in young and middle-aged at these electrodes. Furthermore, the CSD maps showed the appearance of a sink in the elderly group at midline frontal areas that was absent in young and middle-aged subjects. The electrical sources of P2, although more controversial and less studied than those of N1, have been estimated to be located in the supratemporal plane, near those of N1 [16], and the sources of its magnetic counterpart have been located also in the supratemporal plane with opposite orientation to those of N1 [17].

Age-related neuronal loss in superior temporal cortex, and gyral atrophy of the temporal lobes along with degenerative changes in pyramidal neurons of parietotemporal cortex [18,19,20] may lead to changes in the orientation of the source generating P2 and result in the topographical distribution seen in the elderly. The reason why N1 presented the same pericranial distribution in all three age groups is not easy to explain given that its sources are next to those of P2. One possible explanation could be that other structures were participating in or modulating the generation of P2. In line with this there is a report in which P2 dipole orientation changed in a patient with left medial temporal lobe lesions including the hippocampus [21].

The pattern of results shows the existence of ageing-related changes independent of attention which may underlie and influence the changes observed under unattention and attention conditions.

These changes may be related to deficits in frontal cortical inhibitory processes which may interfere with the normal arrest of cortical activity to unattended irrelevant stimuli; cortical folding changes along with some degree of cortical atrophy which may change the orientation of cortical sources, giving rise to changes in scalp recorded potentials; or to a combination of both, mainly in the case of P2 changes observed in this study.

Conclusion

The ageing-related changes in N1 and P2 elicited to attended and unattended irrelevant auditory stimuli were studied in a sample composed of 14 young, 14 middle-aged, and 25 elderly subjects. Ageing affected N1 and P2 irrespective of attention but its effects were different for these two waves. N1 was larger at midline frontal and central electrodes in middle-aged and in elderly subjects irrespective of the attention paid to the stimulation without changes in its topographical distribution. P2 was larger at lateral electrodes in subjects older than 40 years, and it was markedly enhanced over frontal and central electrodes ipsilateral to the attended ear in the elderly, showing a strong lateralization in its topographical distribution. The age-related changes of N1 may be related to inhibitory deficits which become apparent after the fourth decade of age. The age-related changes observed in P2 suggest that its electrical sources may change orientation and that some other areas such as medial temporal structures may modulate its generation.

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