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Auditory event-related brain potentials for an early discrimination between normal and pathological brain aging☆

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Abstract

The brain as a system with gradually decreasing resources maximizes its chances by reorganizing neural networks to ensure efficient performance. Auditory event-related potentials were recorded in 28 healthy volunteers comprising 14 young and 14 elderly subjects in auditory discrimination motor task (low frequency tone – right hand movement and high frequency tone – left hand movement). The amplitudes of the sensory event-related potential components (N1, P2) were more pronounced with increasing age for either tone and this effect for P2 amplitude was more pronounced in the frontal region. The latency relationship of N1 between the groups was tone-dependent, while that of P2 was tone-independent with a prominent delay in the elderly group over all brain regions. The amplitudes of the cognitive components (N2, P3) diminished with increasing age and the hemispheric asymmetry of N2 (but not for P3) reduced with increasing age. Prolonged N2 latency with increasing age was widespread for either tone while between-group difference in P3 latency was tone-dependent. High frequency tone stimulation and movement requirements lead to P3 delay in the elderly group. The amplitude difference of the sensory components between the age groups could be due to a general greater alertness, less expressed habituation, or decline in the ability to retreat attentional resources from the stimuli in the elderly group. With aging, a neural circuit reorganization of the brain activity affects the cognitive processes. The approach used in this study is useful for an early discrimination between normal and pathological brain aging for early treatment of cognitive alterations and dementia.

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Key Words

neural regeneration; aging; auditory stimuli; sensory discrimination; motor task; electrophysiology; event-related potential; sensory processing; cognitive process; grants-supported paper; neuroregeneration

Research Highlights

(1) The study investigated the effects of aging on auditory event-related brain potentials usable for clinical evaluation of perceptual, attention-related and cognitive processes.
(2) The difference of tone-evoked event-related brain potential components was compared between young and aging subjects.
(3) The approach used in this study can be useful for an early discrimination between normal and pathological brain aging for early treatment of cognitive alterations and dementia.

INTRODUCTION

Research on aging has attracted a lot of interest in recent years due to the increased proportion of older people in the world population and its great implications for health care and social and economic life. Alterations in brain activity are considered as the most obvious characteristic of the aging process. The age-related changes in the brain can lead to dedifferentiation and reductions in regional process-specificity[1] and hemispheric asymmetry[2]. The right hemi-aging hypothesis has stated that the right hemisphere shows greater age-related decline than the left hemisphere[3]. In order to explain the increased brain activity in the frontal lobe, Rajas & D'Esposito[3] suggested that deficits in function, dedifferentiation of function, and functional compensation co-occur. This may be caused by the atrophy in the frontal brain regions and this atrophy caused a change in strategy [4]. It can be a compensatory scaffolding process that involves the use and the development of complementary, alternative neural circuits to achieve a particular cognitive goal-a process characterized by adaptive brain behaviour during the whole lifespan[5].

Research on age-related brain alterations has been conducted with electroencephalography[6-11], magnetoencephalography[12-13], functional magnetic resonance imaging[14-15], and positron emission spectroscopy[16]. Electroencephalography studies have considered changes in brain activity mainly in the time domain. By far the most popular and classical electroencephalography time-domain method is the event-related potentials, in which the early modal dependent and obligatory N1 and P2 components contribute to analysis of sensory events, while the later N2 and P3 potentials reflect cognitive processes involving the assessment of stimuli, decision making, strategy selection and recognition memory. Numerous investigations have used not only auditory[6-7, 17], but also visual[18], and somatosensory[19] stimulation paradigms.

The main goal of the study was to characterize the dynamics of the cognitive function in the perception-action loop and how it is related to the physiological changes that occur with age. The study considered the patterns of selective losses and preservation in the processes linked to information flow and storage, like perception, memory, attention, and decision making. We investigated age differences in the behaviour of event-related potentials components in the time domain during auditory discrimination tasks with two tones of different frequencies. A comparatively wide age gap between the young and elderly groups was used because the wide age gap has been shown to be efficient and sensitive to small effects, and at the same time can avoid a possible effect of central nervous system pathology which increases with age[8]. The approach used in this study, aiming at detecting the auditory event-related potentials parameters in a single trial, is useful in the clinical practice due to prolonged human life expectancy and consequent need of an early discrimination between normal and pathological brain aging for early treatment of cognitive alterations and dementia.

RESULTS

Quantitative analysis and general data of subjects

Twenty-eight healthy volunteers participated in this study. The subjects were assigned to two groups according to their age: a young group, comprising eight males and six females with an average age of 26.3 (range 25–31) years, and an elderly group, consisting of eight males and six females with an average age of 55.4 (range 48–60) years. All 28 subjects were included in the final analysis.

Reaction time in auditory discrimination motor task

The right hand reaction time was significantly shorter than the left hand reaction time in the elderly group (mean ± SEM (ms): right hand, 446.54 ± 7.80; left hand, 467.51 ± 7.96; $F_{(1, 628)} = 17.19$, $P < 0.05$), but not significantly in the young group (left hand, 422.56 ± 7.82; right hand, 439.10 ± 8.55, $F_{(1, 630)} = 0.19$, $P = 0.24$). In between-group comparisons, young group presented faster reactions, however significantly only for the left hand (young group, 422.56 ± 7.82; elderly group, 467.51 ± 7.96; $F_{(1, 630)} = 32.87$, $P < 0.001$), but not for the right hand (young group, 439.10 ± 8.55; elderly group, 446.54 ± 7.80; $F_{(1, 630)} = 0.11$, $P > 0.05$).

Event-related potential components

The average amplitude and latency of components for each wave in response to 800 Hz and 1 000 Hz stimulations are given in Figures 1, 2.

The N1, P2, N2, and P3 latencies (Figures 2A, B) were compared with the literature[8, 10, 20]. N1 was defined as the largest negative peak during the interval [80, 148] ms with respect to the stimulus onset and was the same for both age groups.

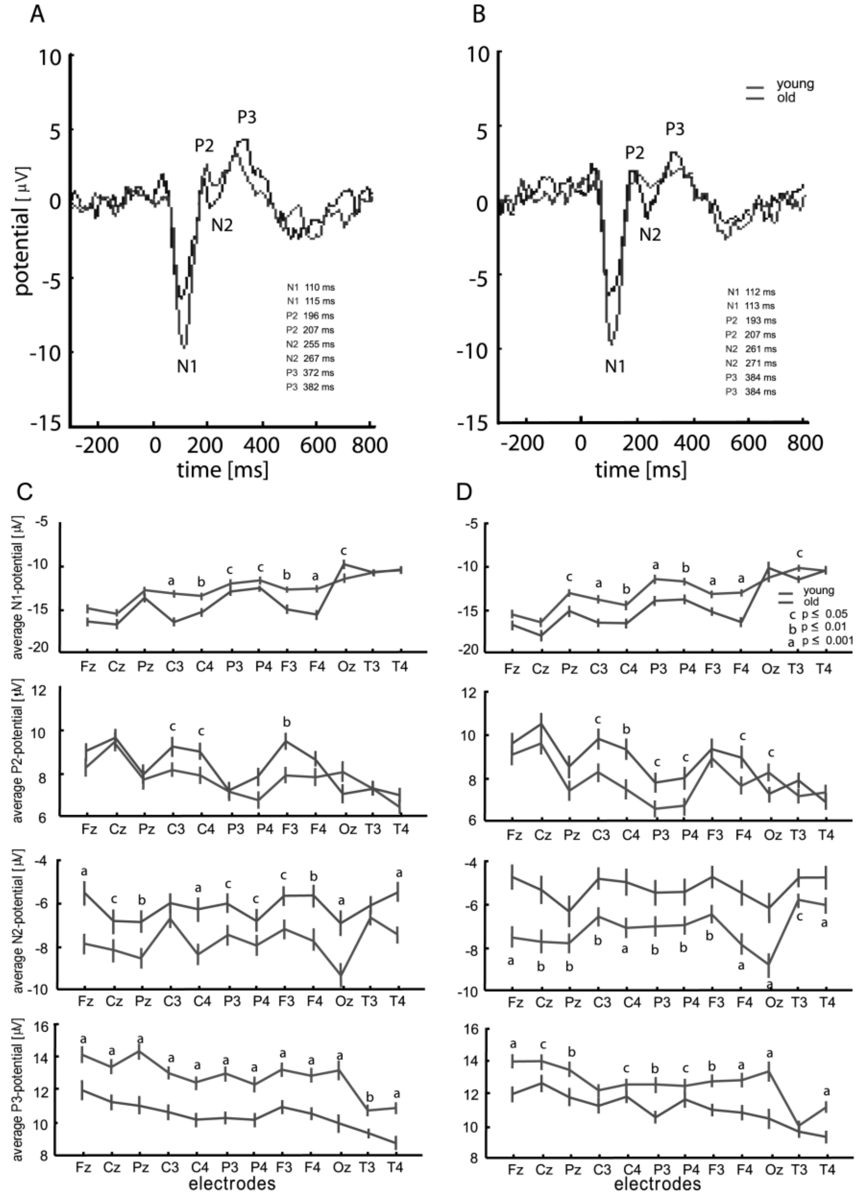

Figure 1 Average event-related potential waves at F3 site for auditory discrimination task in the young and elderly groups.

(A) High frequency 1 000 Hz stimulation (HT); (B) low frequency 800 Hz stimulation (LT). Scalp distributions and statistical comparisons of the amplitude of ERP waves (N1, P2, N2, P3): (C) HT and LT (D) auditory discrimination task (mean ± SEM). The vertical bars represent 95% confidence intervals. $^aP < 0.001$, $^bP < 0.01$, $^cP < 0.05$ for young group *vs*. elderly group (non-parametric Kruskal-Wallis test).

The P2 and N2 peaks of elderly group appeared with some delay as compared to the young group. Due to this delay, the time borders of P2-end/N2-beginning and N2-end/P3-beginning of elderly group were shifted in the time. For the young group, P2 was defined as the largest positive peak during the interval [150, 234] ms with respect to stimulus onset and [150, 248] ms for the elderly group. N2 was the largest negative peak during the time period [216, 310] ms with respect to stimulus onset for the young group and [230, 320] ms for the elderly group. P3 was the largest positive peak during the interval [300, 500] ms for the young group, and [310, 500] ms for the elderly group with respect to the stimulus onset. In common for both tone conditions, the amplitudes of the sensory components (N1, P2) were larger in the elderly group than the young group for either frequency tone. The N1 amplitude was larger in the elderly group than the young group at the motor, frontal, and parietal areas (Figure1; additionally for low frequency tone stimulation at Pz and T3) and the P2 amplitude reached significance only at left frontal and motor areas after high frequency tone stimulation and at the right frontal, motor and parietal areas after low frequency tone (Figure 1; second row).

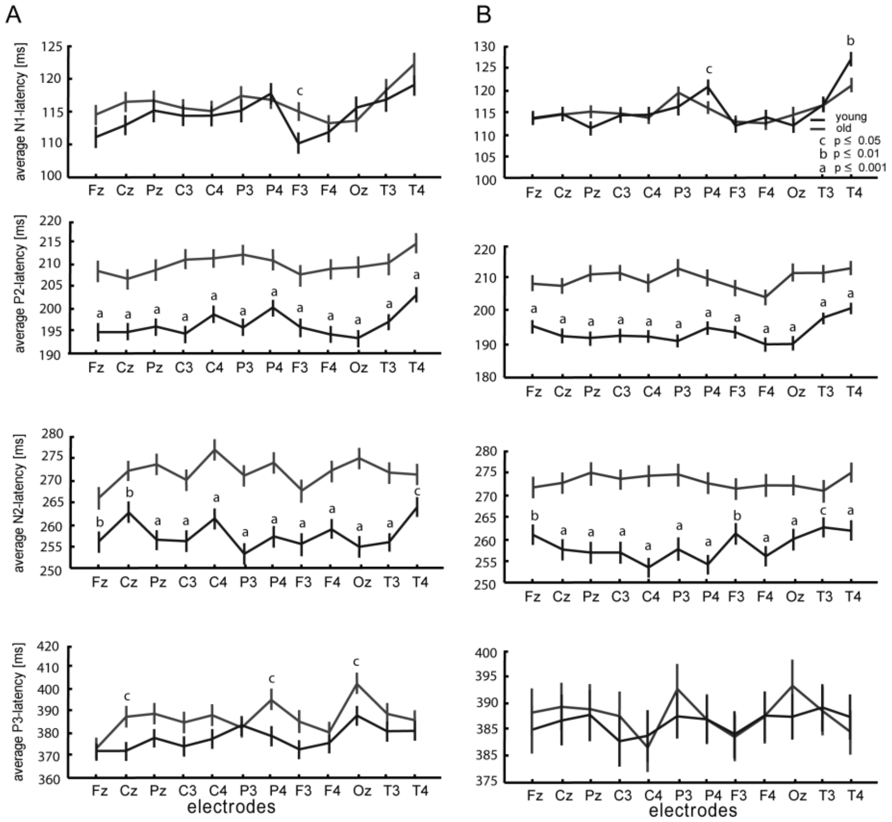

Figure 2 Scalp distribution and statistical comparison of the latencies of the waves recorded for a young and an elderly groups during auditory discrimination task.

(A) High frequency 1000 Hz stimulation (HT); (B) low frequency 800 Hz stimulation (LT). Data are shown as mean ± SEM. The vertical bars represent 95% confidence intervals. $^{a}P < 0.001$, $^{b}P < 0.01$, $^{c}P < 0.05$ for young group *vs*. elderly group (non-parametric Kruskal- Wallis test).

Additionally, the sensory components at Oz had significantly smaller amplitude in the elderly group than the young group in response to high frequency tone for N1 wave and to low frequency tone stimulation for P2 wave. The average amplitude difference between groups was 1.46 μV for high frequency tone and 2.23 μV for low frequency tone. The amplitude distribution of the sensory components was more expressed along the sagittal plane at the vertex than at the central frontoparietal areas. Their amplitude distribution was similar for both hemispheres and more expressed at the sensory-motor area than at frontal and parietal areas.

The sensory components appeared significantly later in the elderly group than in the young group. The delay of the second sensory component was significantly more expressed at all electrodes under either tone condition (Figure 2; second row) and the lag of the first sensory component was expressed at the left frontal area under low frequency tone condition (in the young group, the N1 peak lagged significantly at the right-hemisphere electrodes P4 and T4 by low frequency tone stimulation). The average latency difference between the young and elderly groups was 13.44 ms (high frequency tone) and 15.98 ms (low frequency tone) for P2 component as well 4.70 ms (high frequency tone) and 5.24 ms (low frequency tone) for N1 component. Comparison of sensory component parameters between tones in each age group showed that only latency difference was observed in the young group: the latency of N1 over the right temporal area lagged significantly under low frequency tone condition than under high frequency tone condition and the latency of P2 over the sensorimotor and parietal areas on the right hemispheres lagged under high frequency tone condition than under low frequency tone condition.

At all electrodes under either tone, the amplitude of the cognitive components (N2, P3) in the young group was significantly greater than the elderly group (Figure 1; exception at C3 and T3 for P3 wave under low frequency tone stimulation). Under either high frequency tone or low frequency tone stimulation, the average amplitude difference between the young and elderly groups was

1.77 μV and 1.85 μV for N2 component as well 2.36 μV and 1.69 μV for P3 component. In each age group, the largest N2 potential was observed in the centro-occipital area, but the N2 potential in the centro-occipital area in the young group was greater than the elderly group under each frequency tone. The highest cognitive components were displayed at the head-midline electrodes, although N2 peak was less obvious in the elderly group by low frequency tone stimulation.

In each age group, the average N2 amplitude was greater on the right hemisphere than on the left hemisphere, which was more obvious (with the exception of parietal areas under low frequency tone condition) in the young group than in the elderly group. In each age group, the P3 potential was greater on the left hemisphere than on the right hemisphere in response to high frequency tone stimulation, which was more obvious in the young group area than in the elderly group. The greater P3 potential at the left frontal area than at the right frontal area was only detected in the elderly group after low frequency tone stimulation.

In each age group, the average N2 amplitude was greater on the right hemisphere than on the left hemisphere, which was more obvious (with the exception of parietal areas under low frequency tone condition) in the young group than in the elderly group. In each age group, the P3 potential was greater on the left hemisphere than on the right hemisphere in response to high frequency tone stimulation, which was more obvious in the young group than in the elderly group. The greater P3 potential at the left frontal area than at the right frontal area was only detected in the elderly group after low frequency tone stimulation.

In each age group, the P3 wave over the sensorimotor area was higher on the right hemisphere than on the left hemisphere; and in the elderly group, the P3 wave over the right parietal area was higher than the left area after low frequency tone stimulation.

The latency of the first cognitive component at all electrodes for either tone lagged significantly in the elderly group than in the young group, with an average between-group difference of 13.87 ms for high frequency tone stimulation and 14.51 ms for low frequency tone stimulation (with the exception of C3 and T3 electrodes under high frequency tone stimulation; Figure 2). This tendency was observed for the P3 latency only with respect to high frequency tone at the vertex, right parietal and centro-occipital areas (Figure 2).

Comparison of cognitive component amplitude in each group between tones: In the young group, the N2 amplitude at the head-midline (Fz, Oz), left-hemisphere (C3, P3, T3) and right frontal area in each group was greater under low frequency tone stimulation than under high frequency tone stimulation. In the young group, the N2 amplitude lagged significantly at C4, but was earlier at T3 under high frequency tone stimulation compared to low frequency tone stimulation. In general, the N2 peak in the young group came earlier on the right hemisphere under low frequency tone stimulation and on the left hemisphere under high frequency tone stimulation. In the elderly group, P3 amplitude at the sensorimotor and parietal areas on the right hemisphere under low frequency tone stimulation was higher than under high frequency tone stimulation. In each age group, the P3 peak at the frontal-central areas lagged under low frequency tone stimulation than high frequency tone stimulation and in the young group, the P3 peak at the vertex appeared later under low frequency tone stimulation than high frequency tone stimulation.

DISCUSSION

The effect of age on event-related potential components evoked by the tones both in the active auditory oddball tasks was described in a well-balanced group of normal subjects. The study provided a reliable estimate of the effects of aging allowing comparison between event-related potential waves from early sensory to late cognitive components.

The amplitude and latency of the exogenous components are considered to be related to the stimulus and are indices of the early processing stages (automatically or obligatory). The amplitude of the early sensory component N1 at the frontal, motor and parietal areas was in general larger in the elderly group than in the young group under either high frequency tone and low frequency tone stimulations; under high frequency tone stimulation, the amplitude at the left frontal cortex appeared later in the elderly group than in the young group, and under low frequency tone stimulation, the amplitude at the right parietal and temporal areas came later in the young group than in the elderly group. Six brain processes could contribute to N1 generation: components generated in auditory cortex in a supratemporal plane, in association cortex on a lateral side of temporal and parietal cortices, in motor and premotor cortices, mismatch negativity, and also components generated in temporal and frontal cortices[21].

The first three components, generated in the supratemporal plane, in the lateral side of temporal parietal cortices, in motor and premotor cortices, were considered as ‘true’ N1 components and assumed to be affected by physical and temporal features of stimulus and by the subject state. The latter three components, generated in the temporal and frontal cortices, were believed to be caused not by the stimulus itself, but by the conditions in which it occurs. As long as both age groups were stimulated with the same stimuli, the difference in N1 amplitude could be due to a general greater alertness of elderly group with respect to the acoustic stimuli during early sensory processing. For the same experimental paradigm was reported, frontal N1 amplitude, parietal N1 latency[20] as well as prefrontal and temporal N1 amplitude[22] increase with aging for standard but not targeted tone. Decrement of N1 with stimulus repetition has been explained in terms of habituation or the recovery cycle (refractory period) of the neural generators underlying N1[23]. Hence, one of these processes might be more expressed in the young group. The temporal areas of the elderly group had an opposite sensory processing with respect to tone stimulus and hand movement. Results from this study showed the hemispheric lateralization at the left and right motor areas as well as a higher N1 at the left motor area compared to right motor area in the elderly group under high frequency tone stimulation and suggest either a more widespread activation in the contralateral cortex with increasing age[2-3] when a dominant hand movement is executed, or a hemispheric lateralization in the processing of high- and low-frequency tones respectively in left and right hemisphere[24]. In the elderly group only, an increased brain activity was observed in the frontal area compared to the other brain areas[4]. Similar to our findings, active task performance paradigms such as discrimination[25] and working memory tasks[26] can affect the early sensory component, which has been interpreted in terms of forward suppression[27], repetitive suppression[28], and feedback modulation from downstream neural populations[10, 29].

The late sensory component (P2) had higher amplitude in the elderly group than in the young group over most of the scalp electrodes under low frequency tone stimulation and at a few electrodes under high frequency tone stimulation. The topography of late sensory component appears to be similar across auditory, visual and somatosensory modalities and has been shown to have its maximum value at the vertex[30-31]. The late sensory processing was steadily delayed in the elderly group as the reported effects of aging on the P2 latency with increasing age[7, 32]. Some studies have found that P2 amplitude also increases[8, 33-34]. It has been suggested that P2 latency and amplitude increases are dependent on the electrode position and only apparent at anterior leads[21]. The P2 peak was detected earlier at the right frontal and occipital area for either tone, and above the left motor cortex after high frequency tone stimulation in the young group, and at the right frontal and right motor areas under low frequency tone stimulation and at the left frontal area and vertex under high frequency tone stimulation in the elderly group. The P2 peak over the right motor and parietal areas was significantly delayed under high frequency tone condition in the young group. Under low frequency tone and high frequency tone stimulations, the late sensory component showed a delay in the contralateral hemisphere of the young group with respect to the non-dominant hand movement probably due to the higher cognitive or motor requirements as compared to dominant hand movement, whereas this hand dominant distinction during the sensory stage is diminished or lost with increasing age. The functional role of the late sensory component at the fronto-central sites in an oddball paradigm interpreted as reflecting an attention-modulated process required for the performance of an auditory discrimination task[35]. The P2 wave is linked to a process of sensory gating involved in protecting higher-order cognitive functions by affecting response bias, behavioural inhibition, working memory or attention, and stronger P2 gating as represented by prolonged peak latency leads to better stimulus discrimination ability[35]. Only the results obtained in the elderly group could be explained with the inverse relation between attention and P2 amplitude. The P2 increase with age points to an age-related decline in the ability to withdraw attentional resources from the sensory stimuli; this effect is more pronounced in the frontal areas, as they are most affected by aging[36]. Taken above hypotheses together, the prevalent P2 differences at the frontal areas are linked to the involvement of these brain areas in protecting against interference by irrelevant stimuli[31]. An increase in the level of attentiveness of the subject results in a decrease in P2 amplitude[20, 37]. This modulation has been thought to serve as an index of the ease with which relevant information can be distinguished from the irrelevant information[31].

The endogenous cognitive components develop mostly during later (after 250th ms) post-stimulus time intervals and are thought to represent internal higher brain processes related to stimulus evaluation. The early cognitive component (N2) was higher in the young group than in the elderly group for both tasks at nearly all electrodes, with the exception of the left motor and temporal areas under high frequency tone stimulation. The early cognitive component over the vertex, parietal and occipital cortices was delayed and it was attenuated in the frontal lobe in the elderly subjects[21, 38]. In each age group, the early cognitive component was larger under low frequency tone stimulation compared to high frequency tone stimulation. However, significant differences were observed only at the right frontal area of elderly subjects, whereas for the young subjects, these differences were more widespread: at the centro-frontal, occipital and right frontal areas as well as the left hemisphere (except the frontal area). Thus, larger early cognitive component was obtained when movement with the dominant hand was executed. During the early cognitive processing only in the young group, but not in the elderly group, high frequency tone simulation was faster processed in the left hemisphere and low frequency tone stimulation in the right hemisphere. This finding may be related to hemispheric lateralization with regard to auditory attention and differences in the processing of high frequency tone and low frequency tone stimulations, which is the same as early sensory processing[24]. This suggests that for discrimination processes related to motor tasks, the underlying N2 generation may be lateralized, as reported for P3[39]. Additionally, the right hand reaction time was significantly shorter than the left hand reaction time in the elderly group only. Both age groups were manifested as N2 delay for the left hand motor task under high frequency tone stimulation over the right hemisphere, most prominently over the right motor area and N2 delay for the right hand motor task under low stimulation over the left hemisphere was only observed in the young group. After low frequency tone stimulation, no hemispheric lateralization differences were observed in the elderly group. The functional role of N2 latency has been related to the time needed to make a conscious identification of the stimulus as deviant and the time needed to determine the functional significance of the stimulus amplitude, the time needed to determine the accuracy of this conscious discrimination ability[40-41]. With increasing age, a systematic increase in the N2 latency only[10, 42] or together with a decrease in N2 amplitude have been reported[7]. One interpretation is that the increase in N2 amplitude reflects the existence of an age-related slowing in memory-based comparison processes[43], while another interpretation suggests that the ability of the auditory system to detect stimulus changes attenuates with aging[44].

The late cognitive component P3 was significantly higher in the young group than in the elderly group at nearly all brain areas under either tone and delayed in the elderly group only after high frequency tone stimulation over the vertex, right parietal and centro-occipital areas. With regard to its geriatric modulation, with increasing age, the late cognitive component has been reported to be generally delayed[7, 8, 22, 45]: its amplitude diminished[7, 22] in both auditory and visual paradigms[10, 46], and its scalp distribution altered[8, 22], and its potential field shifted to frontal areas. The P3 delay of the elderly subjects interpreted as slowing of the decision process whether to respond or to inhibit the response when required[46]. It is supposed that age affects both aspects of inhibition in a different manner. Similarly, P3 latency increases with age during auditory stimulus/button-press response paradigm, but not in counting conditions[17]. When comparing low frequency tone and high frequency tone processing, significant hemispheric lateralization differences in P3 amplitude were observed only in the elderly group. Alexander *et al* [39] also reported larger P3 amplitudes over the right hemisphere than the left hemisphere under both target and standard stimuli, primarily at anterior-medial locations (F3/4, C3/4). Compared to high frequency tone stimulation, low frequency tone stimulation produced a delayed P3 peak over the centro-frontal cortex in both age groups, and additionally over the vertex in the young group. The task complexity in terms of P3 amplitude in both groups seems to be either tone-dependent or hand dominance-dependent. The P3 behavior has been reported to depend on stimulus expectation (the less expected stimulus elicits larger P3 amplitude[47]), on selective attention and motivation. The task complexity processing (as represented by P3) was different between the age groups and influenced the involvement of different brain areas.

In conclusion, this study described the effect of aging on the profile of auditory event-related potentials usable for clinical evaluation of perceptual, attention-related and cognitive processes, and provided age adjusted normative data for the clinical use of the spectrum of cognitive event-related potentials evoked by auditory binary motor task. Results from this study showed that with aging, a neural circuit reorganization of the brain activity affects the cognitive processes. This reorganization could be compensatory or a deficit.

SUBJECTS AND METHODS

Design

A non-randomized, concurrent, controlled electrophysiological study.

Time and setting

The experiment was performed at Department of Neurology, Bulgarian Academy of Sciences, Sofia, Bulgaria from November 2010 to October 2011.

Subjects

Healthy volunteers were recruited into this study. All of them were right-handed and without deficits in hearing. Handedness was assessed by a questionnaire adapted from the Edinburgh Handedness Inventory[48]. All subjects gave a written informed consent according to the *Declaration of Helsinki* [49] prior to participating in the study after being thoroughly instructed about the nature of the experiment.

Methods

Experimental set-up

Electroencephalography (EEG) was recorded with a Nihon Kohden EEG-4314F (cut-off frequency of 0.3–70 Hz) using 12 Ag/AgCl Nihon-Kohden electrodes placed on the scalp according to the international 10-20 system: F3, C3, P3, T3; Fz, Cz, Pz, Oz; F4, C4, P4, T4. Simultaneously, hand movement performance was tracked by means of a force profile. The data records were synchronized to the marker of the stimulus onset (–0.5 second before and 1.0 second after the stimulus). An electro-oculogram was recorded from electrodes placed above and below the lateral cantus of left eye for a detection of eye movements and blink artifacts. A ground electrode was placed on the forehead. The skin impedance was controlled to be less than 4 kΩ. A second-order Notch filter was applied in order to discard the 50 Hz AC noise component, using the built-in MATLAB function. The signals were digitized online with a sampling frequency of 500 Hz. The EEG signals were referenced to both mastoid processes. During the measurements, each subject was comfortably seated in an ergonomically designed chair within an electromagnetically shielded Faraday cage.

Subjects were binaurally acoustically stimulated using two pure tones: low frequency 800 Hz stimulation and high frequency stimulation 1 000 Hz. The acoustic intensity was 60 dB. The loudspeakers were situated in front of the subjects. All measurements were executed with closed eyes. Each experimental series consisted of 50 computer generated low frequency (800 Hz) and 50 high frequency (1 000 Hz) acoustic stimuli with durations each of 50 ms and an inter-stimulus interval of 2.5–3.5 seconds. These were presented to the subjects in a randomized order. The task was the bimanual sensorimotor task: while listening to the two acoustic stimuli, subjects were asked to react to the high tones by pressing with the left index finger, or alternatively with the right index finger whenever they heard a low tone. For reacting, subjects were instructed to press as fast as possible with the correct index finger, so that speed and accuracy were given equal importance.

Only artifact-free EEG recorded event-related potentials were processed. Repeatable signals with at least a biphasic component within 1.5 second window with similar shape were termed as auditory event-related potential “waveforms”. Baseline correction was based on the 300 ms long pre-stimulus time period. The parameters of event-related potential waves were computed relatively to the corrected baseline. The signals were later verified to have signal-to-noise ratio (SNR) above mean 1.1. SNRs were calculated using the following formula $\mathrm{SNR} = A/(2 \times \mathrm{SD}_{\mathrm{noise}})$, where the amplitude A is the peak-to-peak voltage of the mean event-related potential, and $\mathrm{SD}_{\mathrm{noise}}$ is the standard deviation of the noise[50]. The noise ε is obtained by subtracting the mean from each individual auditory event-related potential. In other words, for a given single electrode, ε is just the collection of residuals when the mean auditory event-related potential is subtracted from each individual event-related potential and $\mathrm{SD}_{\mathrm{noise}}$ is the standard deviation over this collection.

Auditory event-related potential classification was defined with respect to latency[8, 10, 51]. For each subject, task, electrode, single trials were used to determine the amplitude and latency of N1, P2, N2 and P3 potentials. The exogenous (N1, P2) components are mainly influenced by the external physical stimulus, and endogenous or (N2, P3) components which reflect mostly cognitive processes. N1 is generally viewed as the first negative and often largest peak with a maximum around 100 ms after stimulus onset. P2 is described as the second positive peak with a maximum around 200 ms with respect to stimulus onset. N2 is the second negative peak appearing in the time interval after the P2 up to around the 300 ms. The P3 component is the third positive peak found in the time interval 250–500 ms. The procedure for discarding the single trials of great variability was done separately for the groups. The remaining single trials for each group were used for the analysis of the brain wave components. Their amplitudes and latencies were determined automatically in MATLAB using a procedure based on Global Field Power[51]. The reaction time was determined from the force-time curves.

Pressing with the index finger produced a negative deflection in the force records. Criterion for detection of the reaction onset was a drop of the force curve more than 10% below a baseline, defined for the first 40 ms after stimulus offset.

Statistical analysis

Data were analyzed using the Statistical Package for Matlab version 7.0 (MathWorks Inc., Natick, MA, USA). The amplitude, latency of each ERP component and reaction time were compared between groups for each tone condition by means of non-parametric Kruskal-Wallis test. A level of $P < 0.05$ was considered statistically significant.

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Author contributions: Both Juliana Dushanova and Mario Christov participated in study design, data acquisition, analysis and interpretation, and manuscript writing. Juliana Dushanova was responsible for critical revision of the results. Both authors approved the final version of the manuscript.

Conflicts of interest: None declared.

Ethical approval: The study received full approval by the Local Ethics Committee, Institute of Neurobiology, the Bulgarian Academy of Sciences, Bulgarian.

Author statements: The authors declare the manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application/funding source disputations.

REFERENCES

[1] Baltes PB, Lindenberger U. Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? Psychol Aging.1997;12(1):12-21.

[2] Cabeza R. Hemispheric asymmetry reduction in older adults: the harold model. Psychol Aging. 2002;17(1):85-100.

[3] Rajah MN, D'Esposito M. Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. Brain. 2005; 128:1964-1983.

[4] Greenwood PM. Functional plasticity in cognitive aging: review and hypothesis. Neuropsychology. 2007;21(6): 657-673.

[5] Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol. 2009;60: 173-196.

[6] Goodin DS, Squires KC, Starr A. Long latency event-related components of the auditory evoked potential in dementia. Brain. 1978;101(4):635-648.

[7] Goodin DS, Squires KC, Henderson BH, et al. Age-related variations in evoked potentials to auditory stimuli in normal human subjects. Electroencephalogr Clin Neurophysiol. 1978;44(4):447-458.

[8] Pfefferbaum A, Ford JM, Roth WT, et al. Age-related changes in auditory event-related potentials. Electroencephalogr Clin Neurophysiol.1980;49:266-276.

[9] Morgan CD, Murphy C. Differential effects of active attention and age on event-related potentials to visual and olfactory stimuli. Int J Psychophysiol. 2010;78(2):190-199.

[10] Li L, Gratton C, Fabiani M, et al. Age-related frontoparietal changes during the control of bottom-up and top-down attention: an ERP study. Neurobiol Aging. 2013;34(2): 477-488.

[11] Fjell AM, Walhovd KB. Life-span changes in P3a. Psychophysiology. 2004;41:575-583.

[12] Pekkonen E, Huotilainen M, Virtanen J, et al. Age-related functional differences between auditory cortices: a whole-head MEG study. Neuroreport.1995;6(13):1803-1806.

[13] Pekkonen E, Jääskeläinen IP, Kaakkola S, et al. Cholinergic modulation of preattentive auditory processing in aging. Neuroimage. 2005;27(2):387-392.

[14] D'Esposito M, Deouell LY, Gazzaley A. Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. Nat Rev Neurosci. 2003;4(11):863-872.

[15] Antonova E, Parslow D, Brammer M, et al. Age-related neural activity during allocentric spatial memory. Memory. 2009;17(2):125-143.

[16] Eyler LT, Sherzai A, Kaup AR, et al. A review of functional brain imaging correlates of successful cognitive aging. Biol Psychiatry. 2011;70(2):115-122.

[17] Picton, TW, Stuss DT, Champagne SC, et al. The effects of age on human event-related potentials. Psychophysiology. 1984;21:312-322.

[18] Macpherson H, Pipingas A, Silberstein R. A steady state visually evoked potential investigation of memory and ageing. Brain Cogn. 2009;69:571-579.

[19] Barrett G, Neshige R, Shibasaki H. Human auditory and somatosensory event-related potentials: effects of response condition and age. Electroencephalogr Clin Neurophysiol. 1987;66(4):409-419.

[20] Anderer P, Semlitsch HV, Saletu B. Multichannel auditory event-related brain potentials: effects of normal aging on the scalp distribution of N1, P2, N2 and P300 latencies and amplitudes. Electroencephalogr Clin Neurophysiol. 1996;99(5):458-472.

[21] Zhang F, Deshpande A, Benson C, et al. The adaptive pattern of the auditory N1 peak revealed by standardized low-resolution brain electromagnetic tomography. Brain Res. 2011;1400:42-52.

[22] Anderer P, Pascual-Marqui RD, Semlitsch HV, et al. Differential effects of normal aging on sources of standard N1, target N1 and target P300 auditory event-related brain potentials revealed by low resolution electromagnetic tomography (LORETA). Electroencephalogr Clin Neurophysiol. 1998;108(2):160-174.

[23] Sanmiguel I, Todd J, Schröger E, Sensory suppression effects to self-initiated sounds reflect the attenuation of the unspecific N1 component of the auditory ERP. Psychophysiology. 2013;50(4):334-343.

[24] Ivry R, Robertson LC. The Two Sides of Perception. Cambridge: MIT Press. 1998.

[25] Melara RD, Chen S, Wang H. Inhibiting change: effects of memory on auditory selective attention. Cogn Brain Res. 2005;25:431-442.

[26] Lu ZL, Williamson SJ, Kaufman L. Behavioral lifetime of human auditory sensory memory predicted by physiological measures. Science. 1992;258:1668-1670.

[27] Wehr M, Zador A. Synaptic mechanisms of forward suppression in rat auditory cortex. Neuron. 2005;47: 437-445.

[28] Näätänen R, Tervaniemi M, Sussman E, et al. 'Primitive intelligence' in the auditory cortex. Trends Neurosci. 2001;24:283-288.

[29] Li L, Gratton C, Fabiani M, Knight RT. Age-related frontoparietal changes during the control of bottom-up and top-down attention: an ERP study. Neurobiol Aging. 2013; 34(2):477-488.

[30] Oades RD, Zerbin D, Dittmann-Balcar A. The topography of event-related potentials in passive and active conditions of a 3-tone auditory oddball test. Int J Neurosci. 1995;81(3-4):249-264.

[31] Crowley KE, Colrain IM. A review of the evidence for P2 being an independent component process: age, sleep and modality. Clin Neurophysiol. 2004;115(4):732-744.

[32] Iragui VJ, Kutas M, Mitchiner MR, et al. Effects of aging on event-related brain potentials and reaction times in an auditory oddball task. Psychophysiology. 1993;30(1): 10-22.

[33] Amenedo E, Díaz F. Aging-related changes in processing of non-target and target stimuli during an auditory oddball task. Biol Psychol. 1998;48(3):235-267.

[34] Amenedo E, Díaz F. Ageing-related changes in the processing of attended and unattended standard stimuli. Neuroreport. 1999;10(11):2383-2388.

[35] Lijffijt M, Lane SD, Meier SL, et al. P50, N100, and P200 sensory gating: Relationships with behavioral inhibition, attention, and working memory. Psychophysiology. 2009; 46(5): 1059-1068.

[36] Garcia-Larrea L, Lukaszewicz AC, Mauguiere F. Revisiting the oddball paradigm. Non-target vs. neutral stimuli and the evaluation of ERP attentional effects. Neuropsychologia. 1992;30(8):723-741.

[37] Näätänen R, Michie PT. Early selective-attention effects on the evoked potential: a critical review and reinterpretation. Biol Psychol. 1979;8(2):81-136.

[38] Enoki H, Sanada S, Yoshinaga H, et al. The effects of age on the N200 component of the auditory event-related potentials. Brain Res Cogn Brain Res. 1993;1(3):161-167.

[39] Alexander JE, Bauer LO, Kuperman S, et al. Hemispheric differences for P300 amplitude from an auditory oddball task. Int J Psychophysiol. 1996;21(2-3):189-196.

[40] Novak GP, Ritter W, Vaughan HG Jr, et al. Differentiation of negative event-related potentials in an auditory discrimination task. Electroencephalogr Clin Neurophysiol. 1990;75(4):255-275.

[41] Cooper RJ, Atkinson RJ, Clark RA, et al. Event-related potentials reveal modeling of auditory repetition in the brain. Int J Psychophysiol. in press.

[42] Amenedo E, Díaz F. Automatic and effortful processes in auditory memory reflected by event-related potentials. Age-related findings. Electroencephalogr Clin Neurophysiol. 1998;108(4):361-369.

[43] Verleger R, Neukäter W, Kömpf D, et al. On the reasons for the delay of P3 latency in healthy elderly subjects. Electroencephalogr Clin Neurophysiol. 1991;79(6): 488-502.

[44] Czigler I, Csibra G, Csontos A. Age and inter-stimulus interval effects on event-related potentials to frequent and infrequent auditory stimuli. Biol Psychol. 1992;33(2-3): 195-206.

[45] Juckel G, Karch S, Kawohl W, et al. Age effects on the P300 potential and the corresponding fMRI BOLD-signal. Neuroimage. 2012;60(4):2027-2034.

[46] Hämmerer D, Li SC, Völkle M, et al. A lifespan comparison of the reliability, test-retest stability, and signal-to-noise ratio of event-related potentials assessed during performance monitoring. Psychophysiology. 2013;50(1):111-123.

[47] Picton TW. Human auditory evoked potentials. San Diego, USA: Plural Publishing. 2010.

[48] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971;9: 97-113.

[49] World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Postgrad Med. 2002;48(3):206-208

[50] Suner S, Fellows MR, Vargas-Irwin C, et al. Reliability of signals from a chronically implanted, silicon-based electrode array in non-human primate primary motor cortex. IEEE Trans Neural Syst Rehabil Eng. 2005;13(4): 524-541.

[51] Koenig T, Kottlow M, Stein M, et al. Ragu: a free tool for the analysis of EEG and MEG event-related scalp field data using global randomization statistics. Comput Intell Neurosci. 2011;2011:938925.

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