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Sensory memory during physiological aging indexed by mismatch negativity (MMN)

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Abstract

Physiological aging affects early sensory-perceptual processes. The aim of this experiment was to evaluate changes in auditory sensory memory in physiological aging using the Mismatch Negativity (MMN) paradigm as index. The MMN is a marker recorded through the electroencephalogram and is used to evaluate the integrity of the memory system. We adopted a new, faster paradigm to look for differences between 3 groups of subjects of different ages (young, middle age and older adults) as a function of short or long intervals between stimuli. We found that older adults did not show MMN at long interval condition and that the duration of MMN varied according to the participants' age. The current study provides electrophysiological evidence supporting the theory that the encoding of stimuli is preserved during normal aging, whereas the maintenance of sensory memory is impaired. Considering the advantage offered by the MMN paradigm used here, these data might be a useful reference point for the assessment of auditory sensory memory in pathological aging (e.g., in neurodegenerative diseases).

Keywords: MMN; Auditory memory; ERP; Normal aging

1. Introduction

Physiological aging is commonly associated with a general decline of cognitive skills, including executive functions, memory, visuo-spatial abilities and the speed of information processing. These reductions in cognitive performance probably reflect age-related changes in the brain, which involve several structural and functional modifications during aging (Creasey and Rapoport, 1985). These changes also affect early sensory-perceptual processes (De Sanctis et al., 2008; Fitzgibbons and Gordon-Salant, 1995; Schneider and Hamstra, 1999; Snell et al., 2002) and play an important role in many cognitive processes by functioning as an interface between attention, memory and action (Baddeley, 1996). Mismatch negativity (MMN) is a neurophysiological marker of auditory sensory memory (Näätänen and Winkler, 1999) that is used to evaluate the integrity of echoic memory (Näätänen et al., 2005), learning and the accuracy of the auditory system (Garrido et al., 2009). MMN is elicited when a detectable auditory change or a regularity violation (Winkler et al., 2001) occurs (e.g., an infrequent deviant tone) in a sequence of frequent standard stimuli (Näätänen et al., 1978). MMN arises from an automatic comparison between the current sensory input and the memory trace of the previous tone; this comparison can be accounted for short-term plasticity mechanisms. In healthy subjects, the sensory memory decays after several seconds because MMN is no longer elicited if the stimulus-onset asynchrony (SOA) is longer than 10 seconds (Sams et al., 1993). During that interval, the SOA reflects the ability of the memory system to maintain information.

In comparison with other indexes, the MMN provides several advantages for the study of memory trace decay in aging because it occurs in the absence of attention engagement or task demands. For these reasons, the MMN is particularly suitable for use in a broad range of clinical populations, including patients with pathological aging (e.g., Alzheimer's and Parkinson's diseases), psychiatric disorders and coma (Bronnick et al., 2010; Näätänen, 2003;

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Pekkonen, 2000). Despite the large number of studies on MMN, there is little consensus on whether and how the MMN is modulated during normal aging. An understanding of the natural changes affecting auditory sensory memory during normal aging should be the starting point for all investigations on MMN in pathological aging.

Some studies on MMN in older adults have provided evidence for a reduction of MMN compared with younger groups during short SOAs, which supports a specific deficit in the encoding process of sensory information (Alain and Woods, 1999; Cooper et al., 2006; Czigler et al., 1992; Karayanidis et al., 1995; Woods, 1992). However, this result has not been confirmed by other studies (Amenedo and Diaz, 1998; Gaeta et al., 2001; Gunter et al., 1996; Kazmerski et al., 1997; Pekkonen et al., 1993). Few investigations have explored MMN modulation during long SOAs; these experiments state a general decrease of MMN amplitude (Cooper et al., 2006; Czigler et al., 1992; Pekkonen et al., 1993, 1996). When this reduction was concomitant with a normal MMN during short SOAs, only impairment of information maintenance was suggested (Pekkonen et al., 1993, 1996).

The divergence among previous findings might be attributed to several factors, including differences in experimental design (e.g., SOAs, the probability of deviants), in MMN recording and analysis (e.g., reference electrode) and in the age of the groups. Another relevant confounding variable is generated by the characteristics of the deviant stimulus, which may differ from the standard tone in frequency or duration (Cooper et al., 2006; Pekkonen et al., 1996; Schroeder et al., 1995).

Here, we used a new and faster paradigm, proposed and validated by Grau et al. (1998), that reduces the recording time compared to the classical paradigm by about one-third, which is not a trivial aspect in the testing of patients. By delivering trains of 3 stimuli instead of single tones, Grau et al. (1998) reduced the temporal length of the entire presentation, yet preserving the correct proportion between standard and deviant stimuli. The advantage of the short duration suggests that its potential application in pathological aging is greater than that of the standard paradigm. Thus, we intended to identify normative data about changes in auditory sensory memory during normal aging using this paradigm. In addition, to better characterize any alterations in auditory sensory memory across aging, we studied 3 groups of subjects: young, middle-aged and older adults. Finally, we investigated both the frontal and temporal components of MMN, which have been linked to different cerebral sources and functional roles (Alho et al., 1994; Giard et al., 1990; Opitz et al., 2002; Rinne et al., 2000).

The aim of the present study was to evaluate the presence of any significant alterations in auditory sensory memory during physiological aging by studying the MMN elicited by a duration-deviant stimulus across 3 groups of subjects. To determine whether older adults have difficulty in encoding acoustic stimuli or in maintaining the representation of such stimuli over time (Cowan, 1984), we compared the MMN elicited at short vs long intertrain intervals (ITI) (400 vs 4000 ms).

2. Methods

2.1. Participants

Fifty-four voluntary participants took part in the experiment. They were divided into 3 groups according to age with each group composed of 18 subjects: young (age range from 21 to 40 yr), middle-aged (ranging from 41 to 60 yr) and older adults (ranging from 61 to 80 yr).

Participants underwent a neuropsychological evaluation in order to test their cognitive status. The tests battery assessed language comprehension (Token Test), memory (Digit Span; Spatial Span; Auditory-Verbal Learning Test, immediate and delayed recall; Rey-Osterrieth Complex Figure, Recall; Wechsler Memory Scale), constructional and visuo-spatial abilities (Rey-Osterrieth Complex Figure, Copy) attention and executive functions (Trial-Making Test A and B). All tests were administered and scored according to standard procedures (Lezak et al., 2004). In addition, a brief hearing test was performed on all participants to exclude those who presented sensory deficit. Nine subjects who presented one or more pathological test scores were excluded from the study. Moreover, 3 additional subjects were excluded from the analyses for excessive artefacts during EEG recording. The final composition of the groups was as follows: 15 young subjects (6 males, mean age 33.60 $\pm$ 4.42 yr), 12 middle-aged subjects (8 males, mean age 50.83 $\pm$ 6.60 yr) and 15 older adult subjects (9 males, mean age 68.13 $\pm$ 5.76 yr). Written informed consent was obtained from all participants. The protocol was carried out in accordance with the ethical standards of the Declaration of Helsinki and was approved by the local ethics committee for research in human subjects of the IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy.

2.2. Stimuli and procedure

The stimuli and procedure were the same as those used in Grau et al. (1998) (Fig. 1). Sequences of 3 tones were presented binaurally with earphones. The sequences differed only in the first tone, which could be standard (50%) or deviant (50%). All of the remaining tones were always standard. The overall probabilities of the standard and the deviant tone were 0.83 and 0.17, respectively. The standard tone was a pure sine wave tone of 700 Hz with an intensity of 85 dB SPL (sound pressure level) and a duration of 75 ms. The deviant tone had the same frequency and intensity as the standard tone but a different duration (25 ms). The SOA between tones within the same train was 300 ms.

Every participant completed 2 separate experimental blocks in the same day, separated by five minutes of break. Each block had a short (400 ms) and a long (4000 ms) ITI. The order of presentation of the blocks was balanced be-

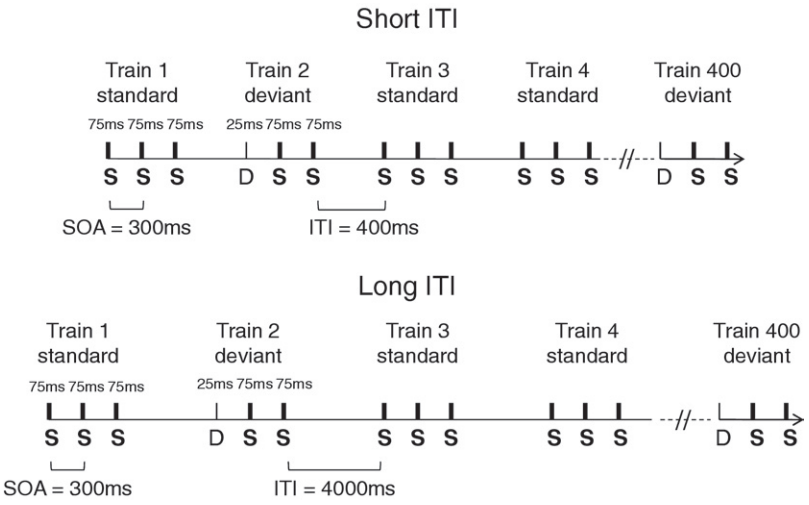

Fig. 1. Schematic representation of stimuli presentation. Sequences (N = 400) of 3 tones were presented randomly (N° standard trains = 200; N° deviant trains = 200). The sequences differed only for the first tone, which could be standard (S = 75 ms, thick lines) or deviant (D = 25 ms, thin lines). The SOA between tones within the same train was 300 ms. The ITI between the beginning of the last tone of the previous train and the beginning of the next tone could be 400 (short ITI upper panel) or 4000 ms (long ITI lower panel) depending on the condition.

tween subjects. In each block, 200 standard and 200 deviant sequences were randomly delivered. The 400 ITI and 4000 ITI blocks had lengths of 7 and 32 min, respectively, including short pauses.

After positioning of the EEG cap and earphones, participants were seated in a comfortable chair in a dimly illuminated room. During the EEG recording, efforts were undertaken to normalize the recording state for all the subjects. Each subject was instructed to watch a silent movie without subtitles, to ignore the auditory stimuli and to avoid extra eye movements and blinking as much as possible.

2.3. EEG recording and data processing

An EEG signal was recorded from 19 electrodes set in an elastic cap (Electro-Cap International, Inc.) that was positioned according to the 10–20 International system. The electrode locations were Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1 and O2. An EEG signal was also recorded from the left and right mastoids (M1, M2). Fpz was used as a ground. The reference electrode was placed at the tip of the nose. An electro-oculogram (EOG) was recorded from 2 bipolar channels placed on the external side of both eyes for the horizontal EOG and above and below the right eye for the vertical EOG. Data were collected with a high cut-off filter of 80 Hz and digitalized at a sampling rate of 250 Hz (BrainAmp MRplus, BrainProducts GmbH, Munich, Germany). The impedance was kept below 5 kΩ.

Event-related potentials were obtained off-line. The EEG recordings were filtered with a pass-band filter of 0.1–30 Hz and divided into epochs synchronized with the first tone of each sequence (standard or deviant). Each epoch was 500 ms in length, including a 100 ms pre-stimulus baseline. Trials with eye movements, blinks and muscle artefacts were excluded from the analysis, as were trials in which the voltage exceeded ±75 μV at Fp1/2, Fz, F3/4, F7/8, Cz, C3/4, T7/8 and M1/2 locations. Averaged responses to deviant and standard tones were computed separately for each subject and for each ITI (400 and 4000 ms).

2.4. MMN analysis

The MMN component was quantified by measuring the mean amplitude of responses evoked by standard and deviant tones in a 150–180 ms time window. This temporal interval was estimated by examining the period over which the MMN occurred in the grand-average waveforms of each group and the ITI condition. Four electrode locations were considered in the analyses, which allowed us to discriminate between frontal (F3, F4) and temporal (M1, M2) MMN. Importantly, the MMN appeared as a negative deflection over the frontal and central scalp sites and as a positive wave over the posterior-temporal regions (Giard et al., 1995; Sams et al., 1993). Thus, we expected an enhanced negativity to the deviant tone relative to the standard tone over the frontal sites and an inversion of polarity over the temporal sites.

Mean amplitudes were analyzed with a repetitive measures ANOVA that tested the group (young, middle age, older adults) as the between-subjects factor and the tone (standard, deviant), ITI (400, 4000 ms), area (frontal, temporal) and hemisphere (left, right) as within-subjects factors. In these analyses, the presence of the MMN component should be reflected by the main effect or interaction of the tone factor. Greenhouse-Geisser correction was applied to control for non-sphericity where appropriate. To assess significant interactions ($p < 0.05$), a Bonferroni correction was applied. Only the corrected probability values are reported.

Because the visual inspection of the grand-average waveforms revealed a different length for the processing of

the acoustic stimuli (standard and deviant) between the groups, we performed an additional analysis aimed at evaluating the duration of the response. A point-by-point Student's *t*-test between the standard and deviant tones was applied in the temporal window of 100–350 ms for every group and every ITI condition (Guthrie and Buchwald, 1991; Murray et al., 2002).

3. Results

3.1. MMN amplitude

As shown in Fig. 2 (A and B), an MMN with a negative polarity in frontal areas and a positive polarity in temporal regions was evoked in the 400 ITI condition in the young, middle-aged and older adult groups [ITI × tone × area $F(1,39) = 16.29$, $p < 0.001$]. No difference in the MMN amplitude was present between groups in the 400 ITI condition (−1.3 μV, −1.7 μV and −1.6 μV for frontal MMN and 1.2 μV, 1.3 μV and 1.1 μV for temporal MMN, respectively, for young, middle-aged and older adult groups).

In the 4000 ITI condition, a frontal and temporal MMN was present only in the young and middle-aged groups. In the older adults, no MMNs were elicited in the frontal or temporal areas, as manifest by the significant interaction ITI × tone × area × group [$F(2,39) = 5.88$,

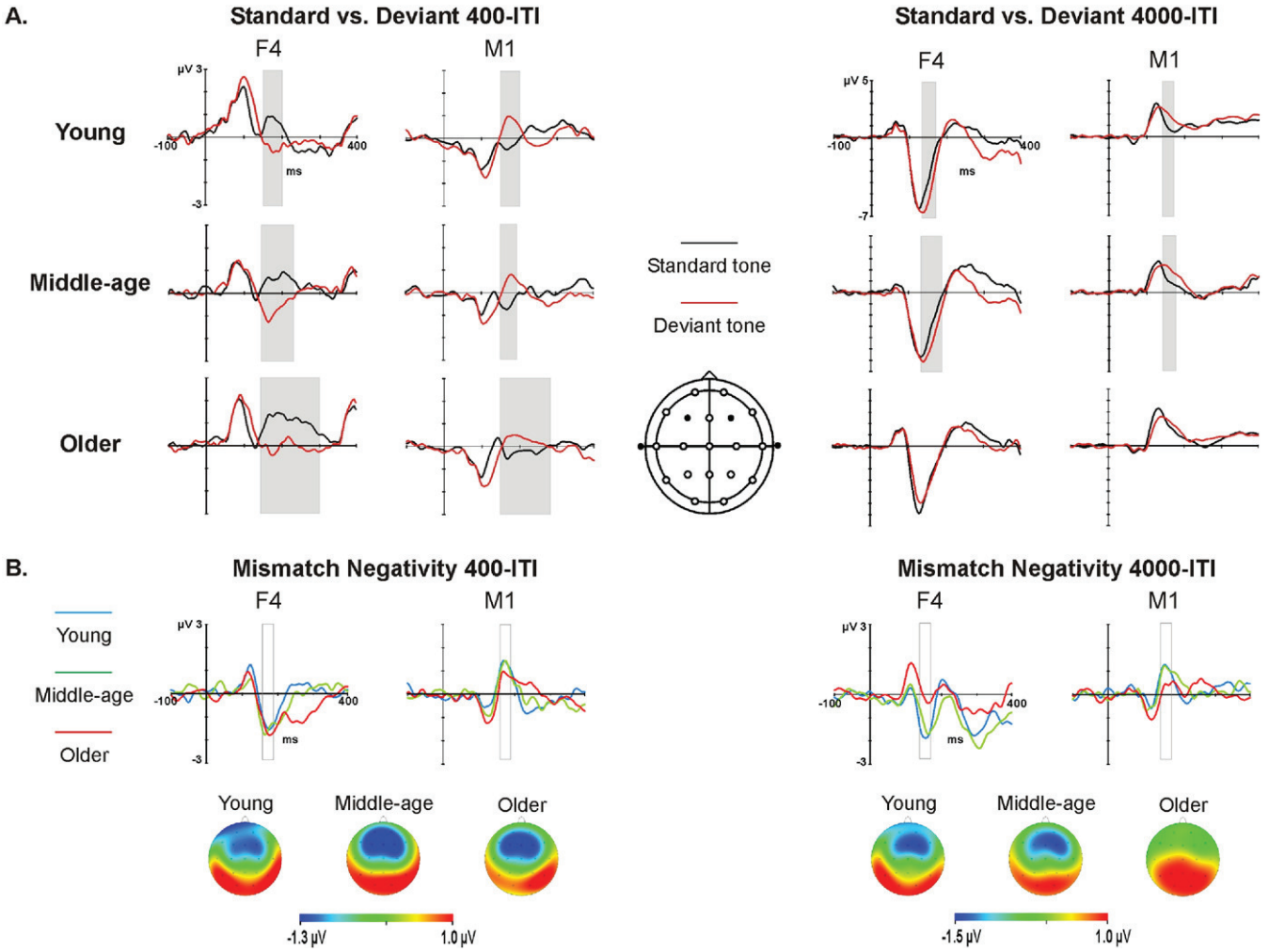

Fig. 2. In Panel A, grand-averaged waveforms elicited by standard (black) and deviant (red) tones are shown for young, middle-aged and older adult subjects. The 400 ITI condition is shown on the left, and the 4000 ITI condition is shown on the right. The signal from 2 electrodes, F4 and M1 is shown for illustrative purposes. Grey boxes superimposed on the waveforms mark significant differences between standard and deviant tones as revealed by point-by-point Student's *t*-tests.

In Panel B, the Mismatch Negativity obtained by subtracting standard from deviant tones is shown for young (in blue), middle-aged (green) and older adult subjects (red). At the bottom, scalp topographies of the MMN amplitude are shown in the time window of 150–180 ms for the 3 groups. The anterior scalp is shown on the top and the right scalp is shown on the right side.

The electrode montage is shown in the middle with the analyzed electrodes shaded black. The polarity of the waveforms is plotted with positive values upward. In both Panel A and B the time point 0 ms is the onset of the standard/deviant stimulus.

$p = 0.006$]. No difference in MMN amplitude was present between the young and middle-aged groups (-1.3 μV vs. -1.4 μV for frontal MMN and 1.0 μV vs. 0.9 μV for temporal MMN areas). It should be noted that an early positivity was present in the older adults group response, that might shape the successive amplitude. Although there was a significant interaction of tone × area × hemisphere [$F(1,39) = 10.21$, $p = 0.003$], no difference was found between the MMN evoked in the 2 hemispheres in any of the groups. Subsequent analysis confirmed that an MMN with an inversion of polarity between the frontal and temporal areas was present in both hemispheres with the same amplitude. No other significant group effects emerged with exception of the interaction tone x hemisphere x group [$F(2,39) = 4.91$, $p = 0.012$], which did not reveal any significant effect of the MMN component in the groups.

Finally, in order to define the relationship between the MMN amplitude and the neuropsychological memory test scores we performed a simple regression analysis, considering the MMN amplitude in both frontal and temporal areas and both ITI conditions (400 and 4000 ms) as dependent variables and the scores of the neuropsychological tests as predictors (Digit Span; Spatial Span; Auditory-Verbal Learning Test, immediate and delayed recall; Rey-Osterrieth Complex Figure, Recall; Wechsler Memory Scale). We had to exclude 3 subjects for this analysis since 2 of the tests used for the neuropsychological evaluation was different then the other participants (i.e., we tested the same cognitive functions but with different tests). Two of the excluded subjects were in the middle-aged group and one was in the older adults group. We found that the higher was the Wechsler Memory Scale (WMS) score, the higher was the amplitude of the frontal MMN in the 4000 ITI condition [$\beta = -0.37$, $t(37) = -2.44$, $p = 0.02$] (Fig. 3). The WMS score also explained a significant proportion of variance in MMN amplitude [$R^2 = 0.14$, $F(1,37) = 5.98$, $p = 0.02$] in frontal electrodes in 4000 ITI condition. No significant results concerning the relationship between MMN amplitude in 400 ITI condition and the neuropsychological tests were present.

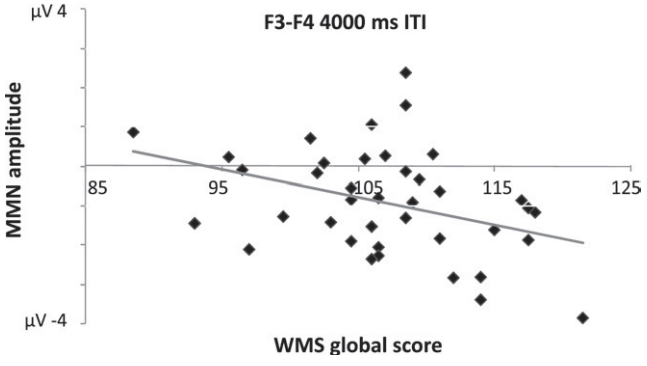

Fig. 3. The scatter plot shows the distribution of the MMN amplitude in frontal area (y-axis) in the 4000 ms ITI condition of all participants as function of the Wechsler Memory Scale global score (x-axis).

3.2. MMN duration

To determine whether the processing of the acoustic stimuli had a different duration between groups, a point-by-point Student's *t*-test was performed to compare the standard and deviant tone responses during the interval between 100 and 350 ms after tone onset (Guthrie and Buchwald, 1991; Murray et al., 2002). Although this analysis did not allow a statistical comparison of MMN duration between groups, it provided a reliable evaluation of the MMN duration within each group, which may be useful for the purposes of the present study. The results of the *t*-tests are marked on the waveforms in Fig. 2A. Surprisingly, this analysis revealed that the duration of the response increased as the age increased, and this was especially evident over the frontal areas. Indeed, in the 400 ITI condition, the first significant difference between standard and deviant tones (i.e., onset) appeared between 144 and 152 ms in all groups, while the last significant temporal point (i.e., the end) was delayed according to the group's age: young ~200 ms, middle-aged ~230 ms, older adults ~314 ms (all $p < 0.05$). The same results were observed in the 4000 ITI condition in groups showing MMN. Indeed, the MMN started at ~138 ms in both the young and middle-aged groups, but it ended at ~166 and ~192 ms, respectively (all $p < 0.05$).

To better explore this relationship between MMN duration and participant's age, we used a simple linear regression analysis considering the average duration of the frontal and temporal electrodes separately. We only examined the 400 ITI condition, given the presence of the MMN in the whole adult age span. Since the previous ANOVA (see *MMN amplitude* session) did not show any significant effects related to the hemisphere, for the regression analysis we considered the mean amplitude of the 2 electrodes in frontal (F3-F4) and temporal (M1-M2) areas. A significant positive relationship was found (Fig. 4). Participant's age significantly predicted the MMN duration in both the frontal [$\beta = 0.47$, $t(40) = 3.37$, $p = 0.002$] and the temporal [$\beta = 0.32$, $t(40) = 2.15$, $p = 0.038$] areas. Moreover, participant's age also explained a significant proportion of variance in MMN duration [$R^2 = 0.22$, $F(1,40) = 11.39$, $p = 0.002$ and $R^2 = 0.10$, $F(1,40) = 4.60$, $p = 0.038$ in the frontal and temporal areas, respectively].

4. Discussion

The aim of this experiment was to evaluate changes in auditory sensory memory during physiological aging using MMN as a neurophysiological index. We adopted a new and faster paradigm (Grau et al., 1998) to optimize this evaluation, which reduced the time required by the traditional procedure. We analyzed the frontal and temporal components of MMNs elicited by a duration deviant stimulus,

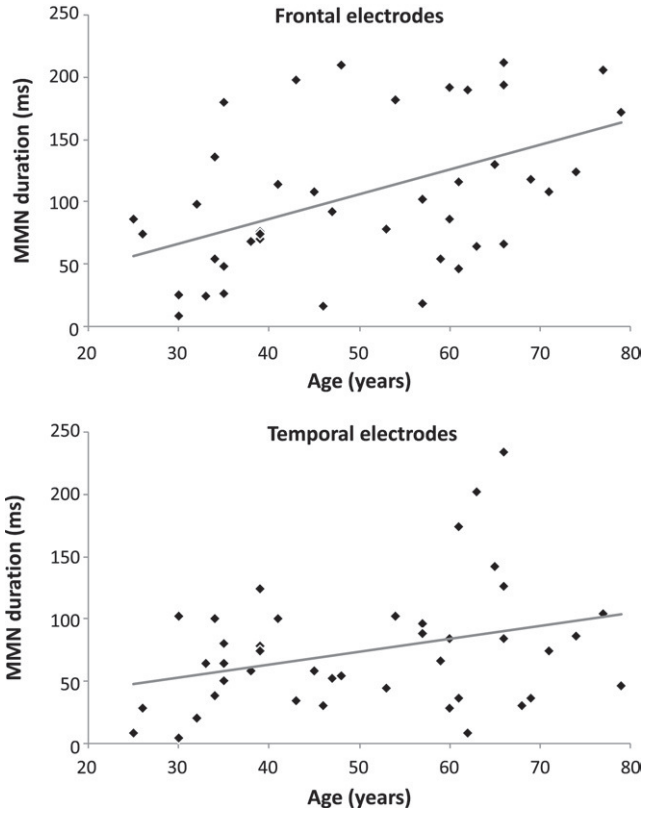

Fig. 4. The scatter plots show the distribution of the MMN duration (y-axis) of all participants as function of age (x-axis), in both the frontal (upper panel) and the temporal (lower panel) electrodes.

looking for differences between the 3 groups of subjects of different ages (young, middle-aged and older adults) as a function of short or long ITIs, i.e., 400 and 4000 ms, respectively.

We found that the 3 groups showed comparable MMNs for short ITIs with the typical negative deflection in frontal areas and inversion of polarity at temporal locations. Conversely, we found a significant difference in MMNs between groups for long ITIs. Young and middle-aged subjects showed similar MMN amplitudes in frontal and temporal sites, but no MMN was recorded in the older adults group at any cortical location.

It is generally believed that the MMN reflects an automatic change detection mechanism that is supported primarily by the perception of the incoming stimulus and by the maintenance of its trace in memory (Cowan, 1984). Recently, Garrido et al. (2009) offered a new theoretical framework (predictive coding) to interpret the MMN that broadens previous positions (Jääskeläinen et al., 2004; Näätänen et al., 1989; Winkler et al., 1996). The authors, Garrido et al. (2009), suggested that, similar to vision, auditory perception is based on "hierarchically and reciprocally organised" neural systems, where abstractions from higher (frontal) cortical areas are matched with data from the lower (temporal) cortical areas through backward connections. At the same time, through forward connections and prediction error signals, lower cortical structures try to adjust the predictions from higher cortical areas based on the actual data. This mechanism continues until the prediction error signal is suppressed and the abstractions from higher cortical areas are optimized (Friston, 2003; Garrido et al., 2009). This perspective offers a new interpretation of the previous MMN data and stresses the dynamic mechanisms underlying MMN generation that involve both primary and higher cortical regions. Indeed, the predictive coding framework allows the integration of numerous studies that have shown a double cortical source for MMN (temporal and frontal locations) (Alho et al., 1994; Giard et al., 1990; Opitz et al., 2002; Rinne et al., 2000) in a unified theory (Garrido et al., 2009) that can account for the functioning of a more complex network.

According to these hypotheses, our results suggest that the sound features were represented and analyzed in the same manner despite the different ages between groups, supporting the conclusion that the encoding phase of auditory sensory memory is not affected by normal aging (i.e., the 400-ITI condition). Moreover, we suggest that, with a brief time lag between the stimuli, the dynamic causal mechanism that involves temporal and frontal locations works properly to optimize the system by reducing the prediction error and refining the abstractions. Conversely, data for the long ITI suggest impairment in the maintenance of the sensory trace with increasing age.

These results are consistent with 2 previous studies that reported a normal aging impairment of sensory memory trace maintenance but not of feature analysis (Pekkonen et al., 1993, 1996). Pekkonen et al. (1993, 1996) studied the MMN elicited by a change in tone frequency, which might rely on slightly different mechanisms compared to the detection of the duration of deviant stimuli.

Cooper et al. (2006) performed the only investigation of the MMN in response to duration changes during a long ITI, comparing young vs. older adult subjects. They reported an MMN in older adults that was reduced in amplitude compared to the MMN elicited in the young group. Although we did not find MMN in older adult subjects, our findings are not in disagreement with those of Cooper et al. (2006). A possible explanation for the discrepancy between findings may be that the long SOA (3000 ms) used by Cooper et al. (2006) was actually shorter than that used in this study (4000 ms as the ITI). Therefore, it is plausible that the representation of the stimulus trace was still present at 3 seconds, although already impaired, and that it decayed at longer temporal intervals, which suggests a linear correlation between the temporal presentation of the stimuli and MMN amplitude. Moreover, another factor that may have affected the results is the age of the older adult subjects recruited in the Cooper et al. (2006) study. The older adults in their study ranged in age between 51 and 79 yr, which partially

overlaps the age range of both our middle-aged (41–60 y) and older adult (61–80 yr) groups.

The study by Cooper et al. (2006) and other investigations of the MMN elicited by a duration deviant stimuli (Alain and Woods, 1999; Czigler et al., 1992; Karayanidis et al., 1995; Woods, 1992) revealed a reduction of MMN in older adult subjects for short SOAs. However, a direct comparison between the present and previous studies is difficult due to methodological differences, such as the stimuli presentation (Pekkonen et al., 1996) and the different features of the paradigm. Here, we adopted the Grau et al. (1998) paradigm, which reduces the duration of the EEG recording compared to the classical MMN paradigm and provides a more practical tool for the investigation of sensory memory in patients. Our data are consistent with those of Grau and collaborators (1998), who applied the new paradigm only to young and middle-aged (range 40–57 yr) groups. They reported an MMN in middle-aged subjects with short ITIs but not when a longer ITI of 5 seconds was used, supporting the idea of memory impairment with increasing age. We extend these previous observations with a more complete investigation of auditory sensory memory in normal aging. Both young and middle-aged subjects maintained the sensory trace for a temporal interval of 4000 ms, but this ability was impaired in subjects over the age of 60 years, and the MMN disappeared both in frontal and temporal areas. When the time lag between the stimuli was increased, the reciprocal interaction between the frontal and temporal areas ceased to serve its function, which is the optimization of auditory system predictions and the reduction of errors. Because we did not record MMNs in frontal or temporal locations at 4000 ITI, we cannot speculate about which subprocess is involved in physiological aging, the abstraction generation or the predictive error reduction.

We should consider that structural, neurochemical and electrophysiological alterations may occur in normal aging (Dickstein et al., 2007). Noteworthy evidence concerning MMN mechanisms is provided by the age-related reduction of glutamate receptors (i.e., GluR and NMDA) in the frontal and temporal cortices of old macaques (Gazzaley et al., 1996; Hof et al., 2002), areas that are involved in MMN generation (Ehrlichman et al., 2008; Heekeren et al., 2008; Javitt et al., 1996; Kreitschmann-Andermahr et al., 2001; Umbricht et al., 2000; Umbricht et al., 2002). Several studies found a strong reduction of the MMN amplitude when NMDA receptors were pharmacologically blocked by the NMDA antagonist ketamine (Ehrlichman et al., 2008; Heekeren et al., 2008; Javitt et al., 1996; Kreitschmann-Andermahr et al., 2001; Umbricht et al., 2000; Umbricht et al., 2002). Interestingly, one of the corticocortical pathways most affected by this receptor decrease, connects the superior temporal cortex and the prefrontal cortex (Gazzaley et al., 1996; Hof et al., 2002; Morrison and Hof, 1997; Vickers et al., 1994), both of which are involved in the MMN generation. Therefore, the absence of an MMN in older adults is in agreement with this line of evidence that suggests an effect of aging on short-term cortical plasticity mechanisms underlying the maintenance of information.

An alternative explanation of our results is related to the ability of the auditory system to generate temporal patterns. Some authors (Cowan et al., 1993; Winkler and Czigler, 1998; Winkler et al., 2001) suggested that MMN is not only generated by the violation of the standard memory trace, but also by the violation of the regularity in the stream of auditory stimuli. Since we adopted a paradigm (Grau et al., 1998) where the stimuli are presented by trains (instead of single tone presentation), it might be that the lack of MMN in the older adults reflects the sensitivity of this population to extract global pattern in a stream of auditory stimuli (perceptual grouping) instead of a memory deficit per se (Winkler et al., 2001). However, we think that, if a perceptual grouping effect was present in our experiment, it should affect both the 400 and 4000 ms ITI conditions, since the grouping should involve the entire train (the regularity is a triplet of standard tones and the violation of this regularity is the deviant train). Furthermore, based on Winkler et al.' results (2001), who tested young subjects, we should expect the presence of the perceptual grouping effect even in the other groups (young and middle-aged groups).

In addition to the effects of aging on the amplitude of the MMN, we also investigated the duration of the MMN in the different groups. Surprisingly, we found that the duration of MMN varied gradually according to the participants' age. MMN had a similar onset between the groups but a different end point that was delayed in an age-related manner. A significant regression analysis also confirmed this positive relationship between participant's age and MMN duration.

In young participants, the standard tone elicited a positive response while the deviant tone elicited a negative response, both of which promptly returned to baseline. As age increased, the positive response elicited by the standard tone took longer to return to baseline. At the same time, the negative response associated to the deviant tone became less negative. The combination of these effects resulted in a longer difference between the 2 tones (MMN duration) as a function of the age. Recent evidence suggested that the positivity induced by the standard tone increases as a function of the number of stimuli preceding the deviant tone (Repetition Positivity) (Baldeweg et al., 2006; Baldeweg, 2006, 2007; Costa-Faidella et al., 2010; Haenschel et al., 2005). In the present study, the positive component related to the standard tone was preserved in the older adults group (or even enhanced) compared to the young and middle age groups. On the contrary, the negativity associated to the deviant tone (evident in the young and middle age groups) disappeared. Unfortunately, in our study we are not able to link the number of standard tones and the amplitude of the relative positive component directly, since we can calculate only the mean amplitude over the entire paradigm (200 standard trains and 200 deviant trains). The MMN duration

might deserve to be investigated in future studies, in the light of the predictive coding perspective, paying attention to the Repetition Positivity effect induced by the standard stimulus (Baldeweg, 2006, 2007). Indeed, the finding about the MMN duration might be attributed also to the underlying activity of the forward connections and prediction error signal, where lower cortical structures try to adjust the predictions from higher cortical areas based on the actual data until the abstraction of higher cortical areas is optimized (Garrido et al., 2009). This trend, which was observed during both short and long ITIs, was stronger over the frontal areas. To our knowledge, our observations concerning the duration of MMN have not been previously described, although Cooper et al. (2006) observed similar effects. The time windows over which the MMN was significantly different from zero showed a delayed end point in the older adults compared with the younger subjects for both the short and long SOAs. Consistent with the notion that a slowing of cognitive functions is generally associated with normal aging, this result suggests that the mechanisms involved in auditory sensory memory take longer as age increases. Based on the predictive coding hypothesis (Garrido et al., 2009), we suggest that aging affects the entire mechanism of sensory interference starting from middle age and particularly affects the top-down abstraction generation process because the duration difference is more evident in the frontal location. Neurophysiologically based interpretations for the delay in the duration of MMN across the tested groups may be derived from an imbalance between excitatory and inhibitory mechanisms, which has been proposed to characterize different cortical regions during aging (Hasher et al., 2007; Hortobagyi et al., 2006; Huttunen et al., 1999). Although neuronal loss is minimal in the normal aging brain, evidence for a decrease in the number of inhibitory synapses has been reported (Brunso-Bechtold et al., 2000; Yankner et al., 2008), which suggests a prevalence of cortical excitability in the older adult brains. Supporting evidence comes from biochemical studies that have shown that aging impairs GABAergic (γ-aminobutyric acid) inhibition in the inferior colliculus and hippocampal cortex (Caspary et al., 1995; Post-Munson et al., 1994) and enhances glutamatergic excitation in the neocortex (Saransaari and Oja, 1995; Wenk et al., 1989). In addition, this altered balance between inhibitory and excitatory neurotransmission may depend on the strong downregulation of many genes involved in inhibitory neurotransmission mediated by GABA (Loerch et al., 2008). With regard to the longer duration of MMN observed during increased aging, we hypothesize that the standard tone elicits a response that promptly returns to baseline as a result of the proper stability of excitatory and inhibitory mechanisms in young adults. Conversely, a weaker inhibitory efficiency and a concurrent persistent excitability could be responsible for the longer time required for the standard tone response to return to baseline with increased aging. This decrease in synaptic efficacy may form the basis for the reduced ability of signal processing, but the neurocognitive interpretation of these results might be considered as a reduction in the speed of information processing.

In summary, the current study provides electrophysiological evidence supporting the idea that the encoding of stimuli is preserved during normal aging but the maintenance of sensory memory for a long temporal interval (i.e., 4000 ms) is impaired. This leads us to conclude that the dynamic causal model (Garrido et al., 2009) is also related to other variables: the time lag between the stimuli and the duration of the memory storage of information. In future studies, it might be interesting to investigate auditory sensory memory with different temporal intervals to determine whether this memory decline linearly correlates with physiological aging. We suggest that the age-related differences in MMN reported here are indicative of genuine differences in auditory sensory memory that may reflect a feature of healthy aging. Considering the advantage offered by the MMN paradigm used here, these data might be useful as a reference point for the assessment of auditory sensory memory in pathological aging, for example, in Alzheimer's and Parkinson's diseases.

Disclosure statement

The authors report no actual or potential conflict of interest. This paper is not under consideration by any other journal and it has not previously published. The protocol has received prior approval by the Ethics committee and an informed consent was obtained from each subject. The experimental procedure conforms to the Declaration of Helsinki. Carlo Miniussi takes full responsibility for the data, the analyses and interpretation and the conduct of the research; as well as access to all of the data. All authors have seen and agree with the contents of the manuscript.

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