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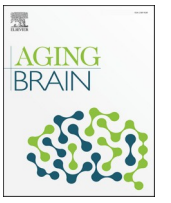

Differences between sub-second and supra-second durations for the assessment of timing deficits in amnestic mild cognitive impairment

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ABSTRACT

Previous studies have often reported timing deficits in older adults with different degrees of cognitive decline, however, the exact nature of impairments in time perception is still to be elucidated. In particular, it is unclear if the deficits are more pronounced for short or long intervals, consistent with notions that different cognitive processes and neuroanatomical areas are involved in the processing of durations of different ranges. The present study aims to further investigate timing abilities in amnestic mild cognitive impairment (aMCI) patients and age-matched controls. Participants were asked to decide whether an acoustic event occurred within the first or the second half of a reference duration. The results revealed a bias towards larger PSE values and reduced precision in aMCI patients compared to healthy controls. Further analyses showed that the bias towards larger PSE values correlated with memory performance, especially when sub-second durations were tested. Overall, the results demonstrate that memory deficits in aMCI patients coincide with changes in time perception in the sub-second interval range.

Introduction

The sense of time is a fundamental aspect of everyday life. It is necessary to coordinate our movements,daily routines, and even communication. However, time perception does not seem to be constant over the human lifespan and can be affected by neuronal changes in the aging brain [1–3]. Deficits in time perception have also been observed in neurodegenerative disorders such as patients with mild cognitive impairment (MCI; [4,5]) and more severe cognitive decline due to Alzheimer's disease (AD; [6–8]). A recent *meta*-analysis showed a medium-to-high effect for AD patients, indicating that they performed significantly worse than healthy controls [8]. When comparing MCI patients and controls, the results are more inconsistent and depend on the patients' age, the range of tested intervals and the timing task employed. Rueda and Schmitter-Edgecombe [9] first investigated temporal abilities in MCI patients and showed verbal underestimation similar to healthy participants when tested with long temporal intervals (around 30 s filled intervals). Coelho et al. [10] also showed similar temporal abilities in MCI patients and healthy controls when tested with long temporal intervals

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(7, 32, and 58 s empty intervals), but in their study participants were explicitly asked to count to track time. However, for MCI patients, subjective time seemed to pass more slowly than it did for controls, and this feeling of time slowing down was significantly correlated with memory deficits (see also [11] using emotional stimuli).

Employing relatively short intervals, Maaß et al. [5] asked their participants to perform two timing tasks, first a time production task with an interval of 1 s, and then a time reproduction task with intervals of 1.17, 1.40 or 1.68 s, and reported specific timing deficits in a group of patients with amnestic MCI (aMCI), a subcategory of MCI patients that are primarily affected by reduced memory functioning [12]. Similarly, Capizzi et al. [4] used brief intervals (0.48–1.92 s) and a time bisection task to investigate time perception abilities in healthy and pathological aging (MCI and AD). The results showed flatter psychometric curves only for more compromised participants (lower cognitive abilities). Taken together, the few studies conducted to investigate time perception in MCI patients seem to suggest different performance depending on the temporal intervals used.

While the exact mechanisms of time perception are unknown to date, many scientists have argued that the underlying neuronal processes differ depending on the length of the tested durations [13–15]. Moreover, the processing of different interval lengths has been associated with different brain regions [14,16].

Temporal processing of short intervals (below 1 s) is frequently linked with motor control, because automatic movements are typically of sub-second durations, whereas the processing of longer intervals (above 1 s) requires the support of additional cognitive resources [13,14]. Studies that have employed both short (in the range of hundreds of milliseconds) and long (in the range of a few seconds) intervals suggested that the cerebellum and basal ganglia are involved in temporal processing independent of temporal range, whereas prefrontal regions seem to be more involved in the processing of long temporal intervals [13,14]. These patterns of results suggest that prefrontal areas may mediate time perception via the role of additional cognitive functions such as attention and working memory.

However, the studies conducted on patients with deficits in these cognitive functions, such as MCI and AD patients, indicate timing deficits when brief temporal intervals are employed [4–6]. For example, Maaß et al. [5] and Capizzi et al. [4] showed decreased temporal abilities in participants with different digresses of cognitive decline when tested with brief temporal intervals. Targeting brief temporal intervals might also help researchers to investigate pure timing abilities avoiding a possible confound of using compensatory strategies like chronometric counting [17–19].

The investigation of temporal processing in MCI is particularly interesting considering the increasing number of patients with cognitive complaints as a consequence of the demographic change in the human population. Patients diagnosed with MCI carry a high risk of developing dementia, and several authors have suggested that timing deficits could serve as a diagnostic marker for pre-clinical states of dementia [5,7,20].

In the present study, a group of aMCI patients and age-matched healthy controls performed a timing task with both sub-second and supra-second durations. As far as we know, no previous studies have directly tested both sub-second and supra-second durations in aMCI patients. Melgire et al. [21] compared sub-second durations and supra-second durations in patients with medial-temporal lobe lesions and found no difference between duration ranges. With respect to AD patients, Caselli et al. [6] reported a specific impairment for sub-second durations, and also Lamotte & Droit-Volet [22] found that age-related decreases in timing performance are more pronounced when probed with shorter intervals.

In sum, several studies in healthy [22] as well as pathologically aged humans [4–6] suggest an impairment for the timing of short intervals. To further investigate this issue, we tested a group of aMCI patients, considering that within this patient group the first sign of cognitive impairment concerns mnemonic functions. Considering that recall memory is known as the key factor in identifying early onset dementia, the word list task of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; [23]) battery was administered. Consistent with previous studies on aMCI patients [4,5] and healthy older adults [18], we expected more pronounced timing deficits in aMCI patients when tested with sub-second intervals.

Methods

We implemented the modified version of a two-interval duration discrimination task, in which a short acoustic event is presented within a longer reference sound and participants must decide whether the event occurred during the first or the second half of the reference duration [19]. Relative to a classical two-interval duration discrimination task (i.e., presenting two durations and asking whether the second duration was shorter or longer than the first one), this task has the advantage of reducing the spontaneous tendency to engage in chronometric counting [19].

Table 1
Demographic information for aMCI and healthy controls.

	aMCI n = 10	Healthy controls n = 30
Gender (female/male)	7/3	16/14
Age		
M (SD); range	71.9 (7.6); 58–81	71.9 (5.4); 60–84
Years of education		
M (SD); range	12.9 (0.3); 12–13	12.9 (0.3); 12–13
Word list recall task		
M (SD); range	−3.2 (1.9); −5.1–0.6	1.0 (2.6); −3.9–6.1

Participants

Ten patients diagnosed with amnestic mild cognitive impairment (aMCI) and 30 healthy controls participated in the study at the German Center for Neurodegenerative Diseases (DZNE Magdeburg, Germany) for monetary reward (Table 1). Diagnosis of aMCI was based on the central criteria of memory complaints and impairment, preserved general cognitive functioning, intact daily activities, and absence of dementia [12]. Diagnosis was assigned via clinical assessment by the DZNE memory clinic, based on standardized psychiatric and neurological examinations, medical history, and neuropsychological testing. Importantly, all participants (patients and controls) underwent standardized clinical assessment, and only participants that were not diagnosed with any form of MCI or dementia entered the control group. The experimental protocol was approved by the DZNE ethics committee, and all participants gave written informed consent. The datasets of three additional participants (from the healthy control group) were excluded from analysis, one due to a misunderstanding of the task and two due to a confusion of the response keys.

Memory performance was additionally assessed with the word list recall task of the CERAD test battery [23]. The CERAD is used as a diagnostic tool to assess cognitive functioning in individuals with risk for developing Alzheimer's Disease or other forms of dementia. In the word list recall task, a list of ten words is presented three times, and after each presentation, the participants repeat as many words as possible. After a delay of about 15 min, during which the participants are occupied with other tasks, they are again asked to recall as many words as possible. From the number of words correctly recalled after the delay (ranging from 0 to 10) we subtracted an individual threshold (specific for age, gender, and level of education; cf. [23]). The resulting score reflects a continuous measure of memory performance. No differences between groups were observed in terms of age and years of education ($p > 0.5$), but groups significantly differed with respect to their score in the word list recall task ($t_{20.9}$ 5.4, $p < 0.001$).

Task, stimuli and experimental conditions

All participants performed a timing task under two conditions, once with sub-second and once with supra-second intervals. Both conditions were presented in separate blocks (counterbalanced order). In every trial, participants were presented with a reference sound of a specific duration and a short acoustic event, positioned approximately in the middle of the reference duration (Fig. 1). The task was to decide whether the acoustic event – a beep signal of 40 ms – occurred within the first or the second half of the reference duration. The study was approved by the local ethical committee and conducted according to the ethical standards laid down in the 6th Revision of the Declaration of Helsinki (Version Seoul 2008). Consent to participate statement: Written informed consent was obtained from participants to participate in the study. A detailed description of this task in comparison to a classical two-interval duration discrimination task can be found in Riemer et al. [19].

The reference duration was signalized by a 450 Hz sound and the beep signal by a 2 kHz sound of 40 ms duration. In each block, containing either short or long intervals, six different reference durations were used. In the sub-second block, the reference durations were 640, 800, 1000, 1250, 1560 and 1950 ms, and in the supra-second block 2440, 3050, 3810, 4760, 5950 and 7440 ms.[1] The beep signal was always presented at one of eight possible time points within the reference duration, defined in percentage values (29, 35, 41, 47, 53, 59, 65 and 71 %). The duration of the beep signal was 40 ms and its middle (not its onset) was set to the specified temporal position within the reference duration. In sum, six reference durations combined with eight relative beep positions were presented in a randomized order, resulting in a total of 48 trials per block. After the offset of the reference sound, participants had to decide whether the beep signal appeared during the first (left button) or the second half (right button) of the reference sound. Responses were given with the two keys at the left and right outermost lower corners of a standard German keyboard. Guided by the experimenter, each participant performed at least six practice trials before each of the two experimental conditions.

Acoustic stimuli were sine wave sounds presented via a PC speaker. During both experimental conditions, participants were instructed to close their eyes and wait until the end of the reference sound before responding. The order of conditions was counterbalanced. No feedback was provided throughout the whole experiment.

Statistical analysis

Responses later than 10 s after the offset of the reference sound were discarded from analysis (1.3 % of all trials). For each participant, two psychometrical functions were calculated based on the data for sub-second and supra-second durations. Logistic functions were fitted using R package *quickpsy* [24] and represent the probability of the response 'beep was in the second half' as a function of the relative position of the beep signal. The first function parameter (50 % threshold) was constrained to range between 0 and 1, and the second function parameter (slope) to range between 0 and 100. Guess and lapse rates were allowed to vary between 0 and 0.1. Bias and precision of temporal judgments were quantified by the point of subjective equality (PSE), defined as the beep position at which the beep was perceived in the second half in 50 % of trials, and the difference limen (DL), defined as half the difference between the beep position at which the beep was perceived in the second half in 25 % and 75 % of trials (i.e., the flatter the logistic function, the larger the DL [25]. Cases in which the DL was more than two times the standard deviation above the mean (indicating poor performance) were defined as outliers and discarded from further analysis (3.8 %). Goodness-of-fit for the psychometric functions was calculated by deviance, ranging from 0.1 to 20.

[1] "Sub-second" and "supra-second" refers to the reference durations divided by two, because the interval between the reference sound onset until the beep signal has to be related to the interval between the beep signal and the reference sound offset.

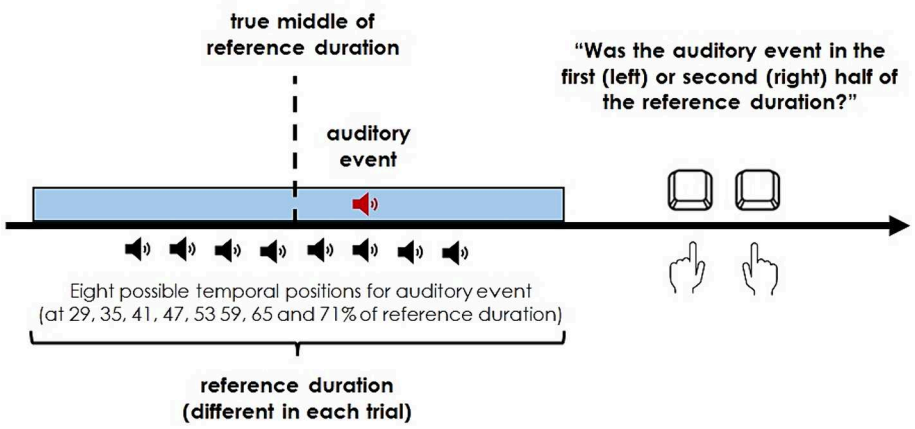

Fig. 1. Schematic representation of the task. Participants were asked to indicate whether an auditory event (red) occurred in the first or in the second half of the reference duration (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

For the analysis of reaction times, responses earlier than 100 ms (0.7 %) or deviating more than three standard deviations from the individual mean of the specific task were discarded (1.2 %).

Data were analysed in R (R Core Team, 2016), by fitting linear mixed effects models (2 × 2 factorial design) using packages *lme4* and *lmerTest*, including *patient group* as between-subjects factor (aMCI vs. control) and *duration range* as within-subjects factor (sub-second vs. supra-second intervals). Subjects were included as random factor. A complete analysis script and the raw data can be found at OSF (https://osf.io/fseh4/).

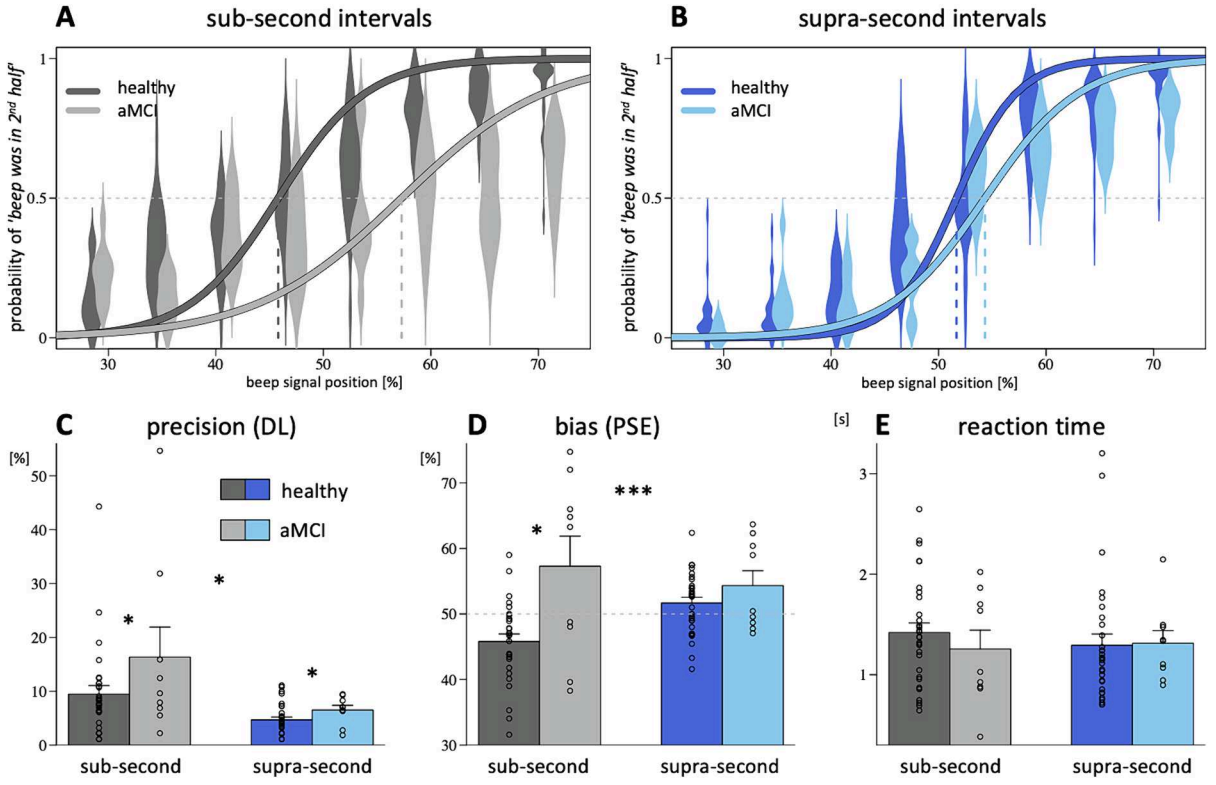

Fig. 2. Logistic functions for **(A)** sub-second interval and **(B)** supra-second intervals as a function of group. **(C)** Precision (smaller DL values indicate higher precision). **(D)** Bias (PSE values close to 50 % indicate higher accuracy). **(E)** Reaction times. Error bars show standard error across subjects. (*** $p < 0.001$; * $p < 0.05$).

Results

The results are depicted in Fig. 2. With respect to the bias of temporal judgments (PSE), we found significant main effects both for *duration range* ($\beta = 0.06$, SE $= 0.01$, $t_{36.3} = 4.0$, $p < 0.001$) and *patient group* ($\beta = 0.11$, SE $= 0.03$, $t_{67.0} = 4.2$, $p < 0.001$), indicating a bias of the PSE towards larger values for supra-second as compared to sub-second intervals, and for aMCI patients as compared to the control group. We also found a significant interaction between *patient group* and *duration range* ($\beta = -0.08$, SE $= 0.03$, $t_{38.8} = -2.7$, $p = 0.010$), indicating that the difference between aMCI patients and healthy controls is more pronounced in the sub-second interval range (Fig. 2D). This was confirmed by subsequent one-tailed t-tests (sub-second intervals: $t_{9.0} = 2.4$, $p = 0.019$; supra-second intervals: $t_{10.5} = 1.1$, $p = 0.15$). Direct comparisons between sub-second and supra-second intervals revealed a significant difference only for the control group (control: $t_{28} = -5.0$, $p < 0.001$; aMCI: $t_7 = 0.3$, $p > 0.5$).

With respect to precision (DL), a main effect of *duration range* indicated that the precision of temporal judgments was significantly higher for supra-second as compared to sub-second intervals ($\beta = -0.05$, SE $= 0.02$, $t_{18.3} = -2.4$, $p = 0.026$). Furthermore, precision was reduced for aMCI patients as compared to the control group ($\beta = 0.07$, SE $= 0.03$, $t_{71.7} = 2.2$, $p = 0.028$). There was no significant interaction between the factors patient group and duration range ($\beta = -0.05$, SE $= 0.04$, $t_{20.5} = -1.1$, $p = 0.28$).

No significant differences were found with respect to reaction times, neither for *duration range* ($\beta = -0.13$, SE $= 0.10$, $t_{37.0} = -1.3$, $p = 0.21$), nor for *patient group* ($\beta = -0.16$, SE $= 0.21$, $t_{58.3} = -0.8$, $p = 0.44$), nor for their interaction ($\beta = 0.18$, SE $= 0.21$, $t_{37.0} = 0.9$, $p = 0.38$).

To test whether the differences in temporal processing between aMCI patients and controls were driven by mnemonic deficits (which were, to a smaller degree, also present in the control group; cf. Table 1), we performed the same analyses with a continuous memory performance score instead of the factor patient group.

The analysis of bias revealed that the PSE was shifted to larger values for supra- as compared to sub-second durations ($\beta = 0.04$, SE $= 0.01$, $t_{36.8} = 3.1$, $p = 0.004$), and also with reduced mnemonic capabilities ($\beta = -0.02$, SE $= 0.004$, $t_{67.5} = -4.5$, $p < 0.001$). Again, we found a significant interaction between *memory performance* and *duration range* ($\beta = 0.01$, SE $= 0.004$, $t_{36.6} = 2.2$, $p = 0.035$), indicating that the effect of reduced memory performance on the PSE shift was more pronounced for sub-second durations. Correlational analyses (Fig. 3) confirmed a negative correlation between memory performance and PSE for sub-second intervals ($t_{36} = -3.7$, $p < 0.001$, r $= -0.52$) and for supra-second intervals $t_{37} = -2.4$, $p = 0.011$, r $= -0.37$).

With respect to precision, the main effect of *duration range* was significant ($\beta = -0.06$, SE $= 0.02$, $t_{17.1} = -3.3$, $p = 0.004$), as well as the main effect of *memory performance* ($\beta = -0.009$, SE $= 0.004$, $t_{72.4} = -2.2$, $p = 0.030$). The interaction was not significant ($\beta = 0.005$, SE $= 0.006$, $t_{17.0} = 0.8$, $p = 0.45$).

With respect to reaction times, neither *duration range* ($\beta = -0.08$, SE $= 0.09$, $t_{37.0} = -1.0$, $p = 0.34$) nor *memory performance* ($\beta = 0.02$, SE $= 0.03$, $t_{57.7} = 0.6$, $p > 0.5$) had a significant influence. Also, the interaction was not significant ($\beta = -0.04$, SE $= 0.03$, $t_{37.0} = -1.4$, $p = 0.17$).

In summary, the analyses based on a continuous measure of memory-related cognitive functioning confirmed the pattern of results that was found for dichotomic groups of aMCI patients and healthy controls.

Discussion

Age-related timing deficits have often been reported, but few studies have specifically investigated these dysfunctions when short

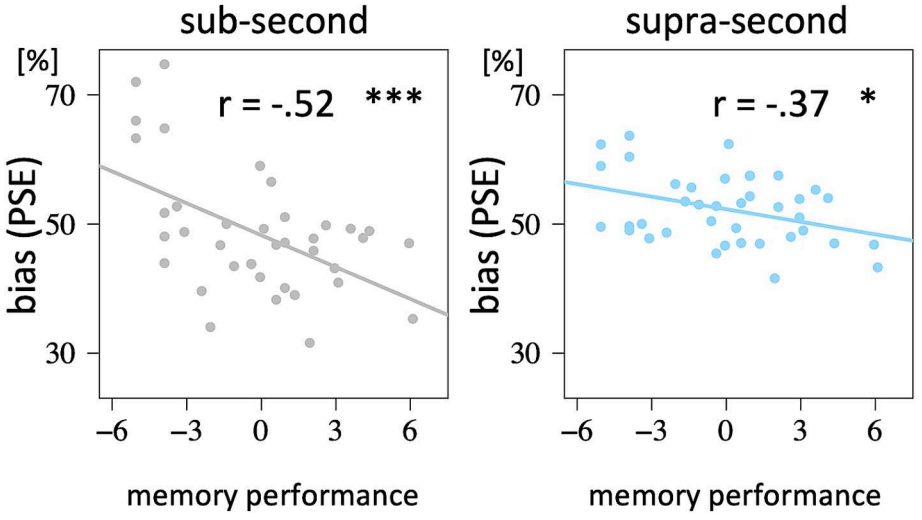

Fig. 3. Correlation between mnemonic capabilities (measured by the word list recall task of CERAD) and the bias for sub-second (left) and supra-second (right) intervals. (*** $p < 0.001$; * $p < 0.05$).

and long temporal intervals are tested within the same experimental design. Consistent with the notion that different neuronal mechanisms subserve the processing of short and long temporal intervals, it is of interest to fully understand if these two processes are differently affected by pathological aging. The present study was designed to answer this question by comparing the timing performance for sub-second and supra-second durations in a sample of aMCI patients and healthy controls. Examining the ability to perceive very short time intervals can provide valuable diagnostic markers for early cognitive impairment. Subtle deficits in time perception may precede more noticeable memory impairments, offering an early indicator of disease progression.

With respect to the bias of temporal judgments, our results show a shift of the PSE towards larger values (indicating that the second part of the reference duration was perceived as longer than the first part) in aMCI patients compared to healthy controls, in particular for sub-second intervals. This pattern of results was confirmed by correlation analyses, indicating that participants with a more pronounced PSE shift were also those with lower memory abilities. There are basically two possible explanations for an erroneous judgment on durations. Either the direct perception of the duration is impaired (based on deficient clock mechanisms), or memory traces of previously perceived durations, against which the current duration percept has to be compared, are compromised. The second possibility was supported by Maaß et al. [5], and it is in line with the notion that MCI patients exhibit increased neuronal loss in the medial temporal lobe, a brain structure involved in memory processes [26]. The PSE bias observed for the aMCI patients in the present study provides further support for the hypothesis that compromised memory traces of durations are at the core of timing deficits in aMCI patients: Assuming increased memory decay for durations in aMCI patients, the memory trace for the first interval (reference duration onset until event) should rapidly fade, so that the second interval (event until reference duration offset) is perceived as longer. This would result in the observed pattern of responses, namely that aMCI patients tended to perceive the event in the first half of the reference duration. However, this explanation contrasts with the observation that the bias to perceive the second interval as longer is more pronounced for sub-second durations, although an effect of memory decay should be larger for longer durations (because there is more time elapsing between the offset of the first interval and the participant's response). Although this inconsistency cannot be reconciled on the basis of the present results, one might speculate about a logarithmic memory decay function, that is, the decay rate could be large at the beginning and scale down over time. As a matter of fact, assuming that the representation of a duration is subject to memory decay does not mean that eventually the duration is memorized as zero (i.e., not having occurred). This way, the proportional difference between the first and the second interval might be more pronounced for shorter durations.

The finding that the PSE shift was more pronounced for sub-second durations corroborates previous observations of timing deficits in MCI patients when short temporal intervals were employed [4,5]. It is also in line with the notion of distinct brain areas and networks involved in temporal processing for short and long intervals [13–15]. This finding might explain why previous studies on MCI patients did not find evidence for timing deficits, because MCI patients were often tested with long temporal intervals [9,10]. Regarding the cognitive and neuronal differences in processing short and long intervals, it has been claimed that processing longer intervals requires the support of additional cognitive resources [13,14] such as attention, working memory and processing speed [27] that are often affected in MCI patients [26]. Moreover, the absence of a timing deficit in MCI patients may appear counterintuitive in reference to studies conducted with AD patients and healthy older adults, showing reduced timing abilities when durations above 2 s were used [8].

It is important to consider that MCI represents a transitional phase between healthy aging and potential conversion into more severe cognitive decline such as AD [26]. Therefore, interindividual differences in the manifestation of cognitive decline might explain the observed differences for short and long durations. It is possible that aMCI patients are still capable of employing compensatory strategies like chronometric counting (see discussion below), which would be effective only for longer durations [17]. Thus, an initial manifestation of cognitive decline might become apparent with very short durations that require higher processing speed for proper evaluation [27]. Corroborating this idea, Mioni et al. [27] tested participants aged between 19 and 87 years and showed that performance depended on the range of temporal intervals (lower accuracy for 0.5 s than 1.5 s), but also that processing speed was the only reliable predictor of age-related changes in time discrimination.

Regarding the results on precision, we observed higher variability for short compared to long temporal intervals in all participants. Moreover, responses of aMCI patients were more variable than controls. Higher variability in duration judgments is often observed in patients, and it is considered a sign of impaired frontally mediated cognitive functions involved in time perception [27,28]. It is possible that patients had difficulty in creating a stable representation of temporal intervals caused by a general cognitive impairment [4]. Our results are in line with a study by Melgire et al. [21] on patients with medial temporal lobe resection. Their results showed that precision of temporal judgments was altered in right medial-temporal lobe patients suggesting that the right medial temporal lobe is involved in controlling the variability of time processing at the level of the decision stage. Also, Caselli et al. [6] reported a specific impairment for sub-second durations. They administered bisection tasks with short (100–600 ms) and long (1000–3000 ms) durations to AD patients and controls and observed comparable performance between groups when tested with long intervals. AD patients showed increased variability (as indexed by increased Weber Ratio) when short intervals were used.

At the behavioural level, some authors have suggested that the different timing performance observed for short versus long durations could be caused by the fact that participants engaged in chronometric counting when the durations to be timed were long enough to support such a strategy, even though they were explicitly instructed not to count. Grondin et al. [17] showed that explicit counting improves temporal performance for durations longer than 1.6 s. This improvement consists in a decrease in temporal variability of time judgments with increasing duration length [17]. Therefore, testing longer durations might be disadvantageous for the detection of timing deficits in cognitively impaired subjects, because chronometric counting might be used as a compensatory strategy. Healthy older adults are often aware of their cognitive deficits. Many studies have shown that humans are capable of temporal error monitoring [29,30], and Lamotte et al. [22] observed that there is a significant correlation between the awareness of being subject to perceptual distortion of time and temporal performance. The more participants were aware of potential distortions in time

perception, the more accurate and precise their temporal judgments were. In accordance with the idea that chronometric counting can be used as a strategy to compensate for existing timing deficits, the results of the present study suggest that the assessment of timing deficits in aMCI patients might benefit from the implementation of sub-second durations. Testing shorter durations might be a more sensitive indicator for timing deficits in pathological aging.

Limitations

A limitation consists in the sample size. The aMCI patient group is quite small, but as reported by Mioni et al. [27], a limited number of studies have been conducted on MCI patients. To further support our results, we conducted additional analyses with a continuous measure of memory functioning in contrast to the dichotomous aMCI diagnosis confirming that the effect of reduced memory performance on the PSE shift was more pronounced for sub-second durations. Considering that MCI denotes a clinical state between normal age-related cognitive decline and AD, our results may offer valuable insight into a supposed gradual progression of timing dysfunctions from normal aging to AD. Therefore, we believe that our study, despite the small sample size, can still provide interesting insight for the understanding of temporal dysfunction in aMCI patients. Additionally, we mention the general description of aMCI patients. Assignment to the patient group was exclusively based on the clinical diagnosis of trained experts at the DZNE memory clinic. Future studies should replicate our findings including additional measures to test the severity of cognitive decline as well as considering other interval ranges and timing tasks.

Conclusion

The results of the present study indicate impaired timing behaviour in aMCI patients for both sub-second and supra-second intervals. This impaired timing behaviour is reflected in a reduced precision and a bias of the PSE towards larger values. The bias of temporal judgments is (i) correlated with cognitive deficits, and (ii) more pronounced for sub-second durations. This is in accordance with the idea of different mechanisms underlying the processing of these temporal ranges. Together with previous studies [6,22], the present results demonstrate that the processing of sub-second intervals is more affected by pathological aging than the processing of supra-second intervals.

CRediT authorship contribution statement

Giovanna Mioni: Writing – review & editing, Writing – original draft, Methodology, Data curation. **Thomas Wolbers:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Martin Riemer:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data are available at OSF (https://osf.io/fseh4/).

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