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Published in:
Behavioral Brain Research

DOI:
10.1016/j.bbr.2019.112110

Publication date:
2019

Behavioural Brain Research 373 (2019) 112110

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Timing deficiencies in amnestic Mild Cognitive Impairment: Disentangling clock and memory processes

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ARTICLE INFO

Keywords:
Interval timing
Memory
Temporal cognition
Aging
Mild cognitive impairment

ABSTRACT

Interval timing performance in cognitive decline is typically characterized by decreased accuracy, precision, or both. One explanation for this decreased performance is a larger clock time variability. However, memory deficiencies associated with cognitive decline might also affect temporal performance in two alternative ways: First, memory deficiencies could lead to reduced encoding of just perceived durations, and thus a stronger reliance on the memory traces of previous experiences (the "prior"), yielding less precise reproductions of the most current experiences. Second, memory deficiencies could hamper the storage of perceived intervals, thus resulting in less influence of the prior.

Here, we present data of 15 patients with amnestic Mild Cognitive Impairment (aMCI) and 44 healthy, aged controls, the latter split in two groups based on memory performance. All participants were tested on a temporal production task to assess clock time variability and a multi-duration reproduction task to assess the influence of memory traces reflecting current and previous experiences.

Patients with aMCI showed the strongest regression towards the mean in a multi-duration reproduction task, followed by low-performing healthy controls and high-performing healthy controls, respectively. As no difference was observed between the groups in terms of clock time variability, and clock variability did not statistically contribute to the observed regression, this increased central tendency effect was not attributable to clock noise. We therefore, in line with the first explanation, conclude that memory deficiencies result in a stronger (relative) reliance on the prior.

1. Introduction

Time perception in humans is pivotal to behavior in a wide range of experimental tasks and real-world contexts. Well-functioning time perception in the sub-second to seconds range is a prerequisite for basic perceptual mechanisms, ranging from perceiving moving objects to successful planning and execution of complex behaviors such as speech production (e.g., [1,2]) and action sequences (e.g. [3]). Given the importance of time perception for general cognitive functioning, it is not surprising that it also has a crucial role in clinical contexts, as seen for example in a number of neurodegenerative diseases that are partially characterized by affected timing (e.g., Parkinson's disease: [4,5]; Huntington's disease: [6,7]; Alzheimer's disease [8–10]). However, as timing is hypothesized to be the product of multiple underlying processes, it is important to carefully discern which components are driving the observed deviations (for discussion, see [30]). Here we assess whether interval timing is also affected in a population with amnestic mild cognitive impairment when compared to age matched healthy controls, and, if so, which underlying processes drive this effect.

Even though contemporary models of time estimation differ in terms of the hypothesized underlying neural implementations, all dissect interval timing into an internal time source ("clock"), memory components, and a decision stage (e.g., [11–15]). Note that the internal time source was traditionally hypothesized to be analogous to a stopwatch that could be explicitly started, paused, and stopped, but most current theories rather assume a neural substrate that predictably changes over time (c.f., [16];). Irrespective of the instantiation, the internal time source represents an internal "clock" as it provides information about the passing of time to other components of the cognitive system. The memory components are typically subdivided into a temporary memory store that contains a representation of the current or the most recently perceived duration ("working memory"), and a

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https://doi.org/10.1016/j.bbr.2019.112110
Received 28 March 2019; Received in revised form 27 June 2019; Accepted 20 July 2019
Available online 21 July 2019

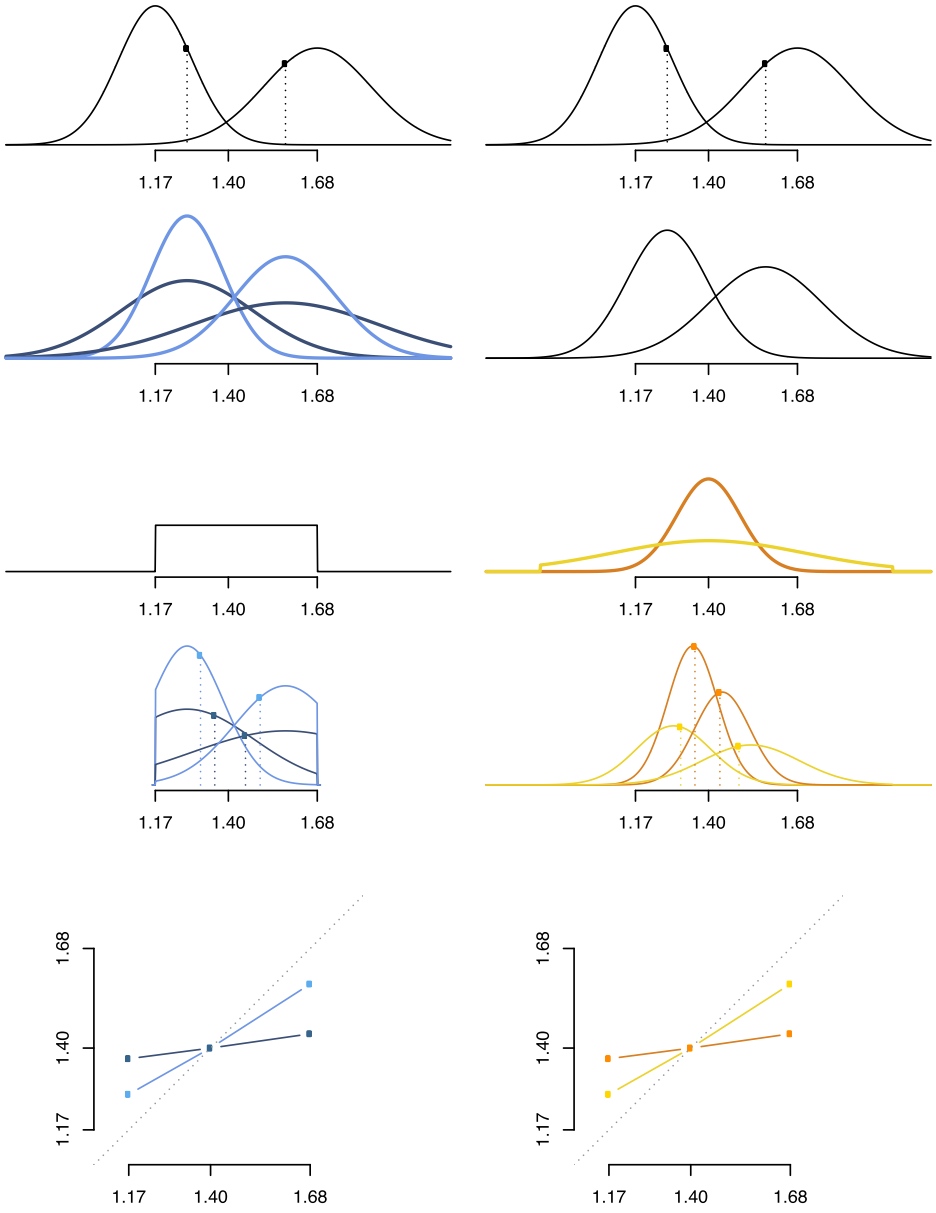

Fig. 1. Schematic representation of Bayesian Inference in interval timing. The left column depicts, from top to bottom, how the width of the likelihood determines the magnitude of the central tendency effect, and the right column depicts how a similar effect can be obtained manipulating the width of the prior. In both columns, the top figure depicts the likelihoods associated with perceived short (1.27 s) or long (1.58 s) durations. The second row depicts the prior, either an uniform prior (left, cf. [36]), or a Gaussian prior (right, cf [37].). The third row depicts the posterior, the integration of likelihood and prior with the dots reflecting the mean of the distribution, which is the resulting estimate. The fourth column shows the resulting central tendency effects. In the left column, the light blue lines reflect a rather narrow likelihood distribution, representing a fairly accurate internal clock. The dark blue lines represent a more noisy clock, resulting a stronger central tendency effect. In the right column, the yellow lines represent a wide, and thus uninformative prior, resulting in a relatively small adjustment of the original likelihood. The orange lines represent a more constrained prior, resulting in larger adjustments, and thus a larger central tendency effect.

long-term memory store in which previous duration representations are stored ("reference memory"). Even though decision criteria play an important role in timing processes (see for a model in which timing is instantiated as a decision process [17]), here we assume – as in common in the interval timing literature – that the main source of variability in simple timing tasks is associated with the clock and memory stages.

Given the prominent role of memory in time perception [18] and specifically the implicated necessity of working memory and episodic memory in temporal performance [19–21] we chose to test a population marked by an isolated episodic memory deficit. These deficits in episodic memory are highly salient markers of developing dementia and Alzheimer's disease, affecting both short- and long-term memory. These markers are critical in the identification of early stages of developing dementia, with impaired performance on memory recall tasks being defined as a hallmark of the development of Alzheimer's disease [22]. A precursor to dementia and AD is Mild Cognitive Impairment (MCI), an intermediate clinical state between normal cognitive decline due to aging and dementia. Within the MCI population, amnestic MCI (aMCI) individuals form a subgroup that is primarily marked by poor performance on neuropsychological tests of episodic memory. Thus, aMCI individuals constitute a well suited population for the study of affected time perception that is specifically caused by memory deficits.

Interestingly, a prominent view in the literature posits that timing deficits related to cognitive decline, in both healthy and pathologically aged populations, are driven by changes in the clock. These changes either result in a decreased accuracy or a slowing-down (e.g., [23–268,27–29], for an extensive review, see [30]). However, as discussed in Paraskevoudi et al. [30], previous research in this field is typically based on paradigms such as bisection or reproduction tasks, that involve both clock and memory components (see also [18]). As these paradigms lack the sensitivity to discern between deficits in clock and memory functions, it is difficult or even impossible to disentangle the relative roles of both processes (see, for example [8]).

Thus, to understand how these neurodegenerative diseases, specifically the memory deficits observed in aMCI, compromise timing processes, it is essential to assess whether clock or memory deficiencies are the source of changes in timing behavior. Here we present a study which aims to disentangle the role of clock variance and temporal memory processes in aMCI patients by assessing the accuracy of the clock and the influence of memory processes on interval timing separately using two paradigms.

The first paradigm entailed a production task in which subjects were asked to terminate a tone by a button-press after one second had passed [18]. As this task uses a highly entrained interval, it is hypothesized that memory updating plays little or no role in the observed performance, which means that the observed variance is a clean assessment of clock noise. The second paradigm consisted of a time reproduction task composed of three different intervals. Typically, in tasks using multiple intervals, a regression towards the mean or central-tendency effect can be observed, with shorter and longer durations systematically biased towards the mean of the presented intervals. This memory phenomenon is highly robust (e.g. [31,32]), and is observed in a large number of domains characterized by noisy, continuous measures (e.g., distance reproduction tasks, [33]; distance and angle estimation, [34]; object size recognition [35]).

This central-tendency effect can be described in terms of Bayesian inference in which the perceived duration (referred to as the likelihood) is integrated with previously perceived intervals that are stored in the reference memory (the prior) [14,36]. When the likelihood is narrow, reflecting a very accurately perceived duration, the influence of the prior will be small, resulting in less central tendency and vice versa. For example, in highly trained professional musicians, such as percussionists, auditory durations are reproduced to perfection, indicative of a peaked likelihood during perception, resulting in a relatively small influence of the prior [37]. Similarly, a number of studies have demonstrated that phenomena such as the intrinsic noisiness of the clock as a function of interval length (i.e., the scalar property, see [36]), or externally manipulated noise in interval timing tasks (audio vs. visual intervals [38],) are well captured by assuming a more uncertain, thus wider likelihood for noisier measurements. Because of the wide likelihood, the prior takes precedence, reflecting a strong reliance on prior memories of similar intervals (see Fig. 1, left panel, and see https://vanrijn.shinyapps.io/MaassVanMaanenVanRijn2019/, for a simulation demonstrating these effects). A similar pattern of effects can be observed when a non-uniform prior (cf. [37]; also see [33]) is used, and one assumes that priors can differ in the second central moment. For example, when a fairly narrow prior is assumed, a relatively strong central tendency will be observed (see right panel of Fig. 1), and vice versa, when a broad prior is assumed, the posterior will be more similar to the likelihood, resulting in a smaller central tendency effect.

In terms of this Bayesian framework, temporal performance of clinical populations (e.g., PD: [25,39]; AD [23,26]:) that are assumed to be associated with an increased clock noise should be characterized by a wider likelihood, and thus a stronger reliance on the prior. However, if a clinical population is marked by memory deficits, an open question is how this deficit influences the integration of the likelihood and the prior. That is, memory deficits could either lead to a less accurate representation of the perceived interval (i.e., a wide likelihood), yielding a relatively strong influence of the prior, and thus a strong central tendency effect. However, as the prior is assumed to be based on a representation of previously perceived durations, one could also assume that memory deficits prevent the construction of an accurate prior. As this would result in the construction of a very wide, uninformative prior, the likelihood is less affected by previous experiences, and thus a highly reduced central tendency effect is expected. Thus, depending on the locus of the impact of the memory deficiency, we either expected a stronger central tendency effect (in case the likelihood is less effectively retained) or a weaker central tendency effect (in case an uninformative prior is formed).

With this study, we addressed two main questions. First, we aimed to assess the role of clock variability in time perception in an aged population, and especially whether clock variance is increased in an aged clinical population marked by memory deficits. Second, we assessed which memory aspect involved in time reproduction is affected in a memory impaired population, providing both insight in the memory mechanisms underlying interval timing and more insight in the memory deficiencies associated with cognitive decline.

2. Methods

2.1. Participants & exclusion criteria

Fifteen subjects with the diagnosis of amnestic Mild-Cognitive Impairment (aged 58–81, M = 72.9, SD = 6.4; seven females) as well as 44 healthy aged controls (aged 60–84, M = 72.2, SD = 5.1; 24 females) completed the experiment at the German Center of Neurodegenerative Diseases (DZNE Magdeburg, Germany) for a monetary reward. The patient group was clinically assessed at the memory clinic of the DZNE by means of their medical history, a psychiatric and neurological examination and neuropsychological testing. All subjects gave written informed consent to participate in the experimental protocol, approved by the local ethics committee. The data of three participants (two of them aMCI individuals) were removed due to not following or not being able to follow task instructions. Outlier threshold were set at 500 and 2500 ms, trials exceeding these criteria were removed from further analysis. For three participants (all aMCI individuals) were removed from further analyses as more than 25% of all their trials had to be excluded. These criteria resulted in 1.2% removed data for the remaining participants. One participant misunderstood the instructions during the first block of the reproduction experiment, and all responses during that block were excluded, yielding a total of 1.6% of excluded cases. The remaining data set consisted of 10 aMCI individuals (aged 58–81, M = 72.9, SD = 7.7; five females) and 43 healthy controls (aged 60–84, M = 72.0, SD = 5.1; 23 females).

2.2. Apparatus

A MacBook Pro (13”, 2011) controlled all experimental events. Auditory stimuli were presented through headphones (Sennheiser, HD280 Pro), with volume adjusted to comfortable levels, as determined by the participant. The experiment was programmed using Psychtoolbox-3 [40–42] in Matlab R2014b.

2.3. Procedure

The first paradigm of the experiment, the one second production task, consisted of 20 trials. Each trial commenced with an intertrial interval (ITI) with the presentation of a fixation cross “+” for a random duration between 2 and 3 s sampled from a uniform distribution. Then a “?” appeared on the screen and simultaneously a 440 Hz pure tone started. The task was to end this tone by pressing a button (SPACE) after one second had passed. Participants were instructed not to count, an instruction that has been shown to prevent influences of chronometric counting [43], or to keep track of time in any other way (e.g., tapping).

The second paradigm, the interval reproduction task, consisted of four blocks of 30 trials each. Each trial consisted of a duration perception phase and a duration reproduction phase. The durations presented were 1.17, 1.4 or 1.68 s. Each trial commenced with an ITI of a random duration between 2 and 3 s sampled from a uniform distribution during which a fixation cross (“+”) was presented in the center of the screen. Then a “!” appeared on the screen for 700 ms to prepare the subjects for the perception phase. Following this, the perception phase of the trial started in which a 440 Hz pure tone was presented for the duration associated with the current trial. Within each block of 30 trials, all 3 durations were presented 10 times, in random order. After completion of the tone, an inter stimulus interval (ISI) of 1.5 s was presented with a “?” displayed on screen. Then another 440 Hz pure tone was started. The task was to press the spacebar when the duration presented in the perception phase had passed (Fig. 2).

2.4. Cognitive assessment

To assess general cognitive functions, all participants completed the Montreal Cognitive Assessment (MoCA, [44]). This tool covers a variety of cognitive functions, including visuospatial abilities, language tasks, memory functioning, and attention. The MoCA scores were used as a

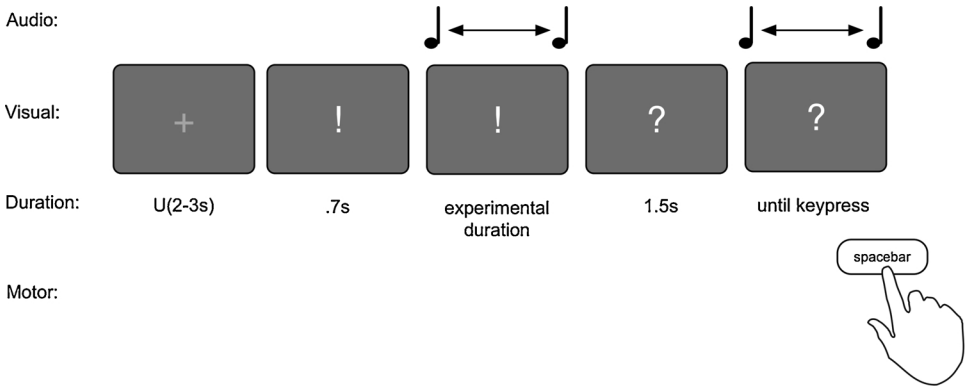

Fig. 2. Graphical depiction of the second experimental paradigm of the experiment.

covariate to partial out general cognitive decline. For the assessment of memory functioning, we administered a subset of the test battery developed by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD [45]). The CERAD is a diagnostic tool to evaluate cognitive functioning in individuals at risk of developing AD or other milder forms of cognitive decline. As this study's aim was specifically to investigate memory functioning, and as recall memory is said to be the key factor in identifying early onset dementia [22,46], only the word list task (learning, recall, recognition) of the CERAD test battery was administered.

2.5. Statistical analysis

The data and all analyses and results can be found at https://osf.io/9xzwn/. As we are interested in comparing performance between healthy controls and participants diagnosed with aMCI, it is of equal importance to be able to assess the reliability of similarities and differences between subgroups. We therefore primarily report Bayesian analyses, as Bayes factors provide a more straightforward interpretation of the likelihood of the presence or absence of differences between groups than traditional analyses. All analyses were performed with the R package BayesFactor (version 0.9.12-4.2; [47]) using the default prior settings, and were interpreted based on the guidelines provided by [48], as adapted by [49]). The reported Bayes factors summarize the extent to which an observer's opinion of the tested variable should change based on the data. Bayes factors of 1 are inconclusive, as it indicates that there is equal evidence for the hypothesis that the variable does have an influence, as there is for the hypothesis that it does not have an influence. Bayes factors larger than 1 represent evidence for the alternative hypothesis of an influence of the tested independent variable on the dependent variable, and Bayes factors less than 1 represent evidence for the null hypothesis of no effect of the tested variable. For the correlation analyses, we report Bayes factors based on [48]) test for linear correlation (see [50]). For the Bayesian linear mixed effect models, we built models predicting centered estimated duration by the entered effects, including participant as random factor. We then assessed the factor of interest by comparing the Bayes factor of the model including the factor with the Bayes factor associated with a model omitting this factor. To facilitate interpretation, we invert Bayes factors below 1 and describe in the text whether the Bayes factor is evidence for inclusion or exclusion of the factor. This way, all reported Bayes factors express the evidence for presence or absence of an effect as values progressively greater than 1.

3. Results

3.1. Questionnaire data

The average score on the MoCA test was 25.7, out of a maximum of 30, with the participants earlier diagnosed with aMCI scoring 23.2, and the healthy controls 26.3. The left panel of Fig. 3 depicts the score on the CERAD delayed word recall task as a function of age, with the larger circles representing participants diagnosed with aMCI, and color coding for participants passing or failing the CERAD word list criterion. The CERAD threshold is based on the age of the participants, but also takes educational background and sex into account. As a relatively large number of healthy controls failed the CERAD recall criterion, we decided to split the healthy control group based on meeting the CERAD criterion into a $controls_{passed}$ (N = 25, aged 60–85, M = 72.0, SD = 5.1, 12 female) and a $controls_{failed}$ (N = 18, aged 60–84, M = 72.1, SD = 5.6, 11 female) subgroup. Even though the $controls_{failed}$ subgroup has no clinical indication of memory deficiencies, the score on the CERAD test suggests that their memory-related performance should be either similar to the aMCI subgroup, or be in between the aMCI and $controls_{passed}$. The right panel of Fig. 3 depicts the MoCA scores as a function of age, with the dashed line depicting cut-off score, with equal color coding as the left panel. Note that the MoCA score is corrected for years of education, but not for age. Interestingly, one (out of 10) of the aMCI participants scored above the MoCA threshold of 25 points, and 14 (out of 43) of the controls scored below the threshold. Even though this could suggest that the aMCI status of some of the participants in the "healthy" control group might need to be re-evaluated, more extensive tests would be necessary before these participants could be categorized as clinically amnesic. We therefore opted for following the aMCI categorization based on the more extensive test battery conducted at the memory clinic, but have split the healthy control group into a subgroup passing and failing a memory test (see below). Results of the Bayesian correlation indicate very strong evidence (BF = 52.75) in favor of a positive moderate association between MoCA and CERAD recall scores (r = 0.42, MAD = 0.12, 90% CI [0.21, 0.62]). In all subsequent analyses, we will cluster performance based on aMCI status, and for the healthy controls, on whether they passed the CERAD Word Recall threshold.

3.2. Assessing clock variability

Clock variability was assessed by the one second production task. As no feedback was given, the average reproduced durations provide an index of the accuracy of the internal representation of 1 s. The first 4 trials were considered start-up trials, and were removed from further analyses. For the aMCI group, average production was .72 s (SD = .37), for $controls_{failed}$ 1.07 s (SD = 1.07), and .79 s (SD = .43) for $controls_{passed}$. The Bayesian analysis was inconclusive, resulting in anecdotal evidence (BF = 1.65, ± 0.03%) for group predicting estimated duration. Addition of age as covariate however, entered both as main effect and as interaction with group, did provide moderate evidence for group predicting estimated duration (BF = 3.75, ± 0.90%). Inspection of the posteriors indicated that this was driven by small positive effects of age in the aMCI and $controls_{failed}$ (both estimated at .01), and a small negative effect of age in the $controls_{passed}$ group (−.02). Given the main effect of age (.01), this means that in the two memory affected groups

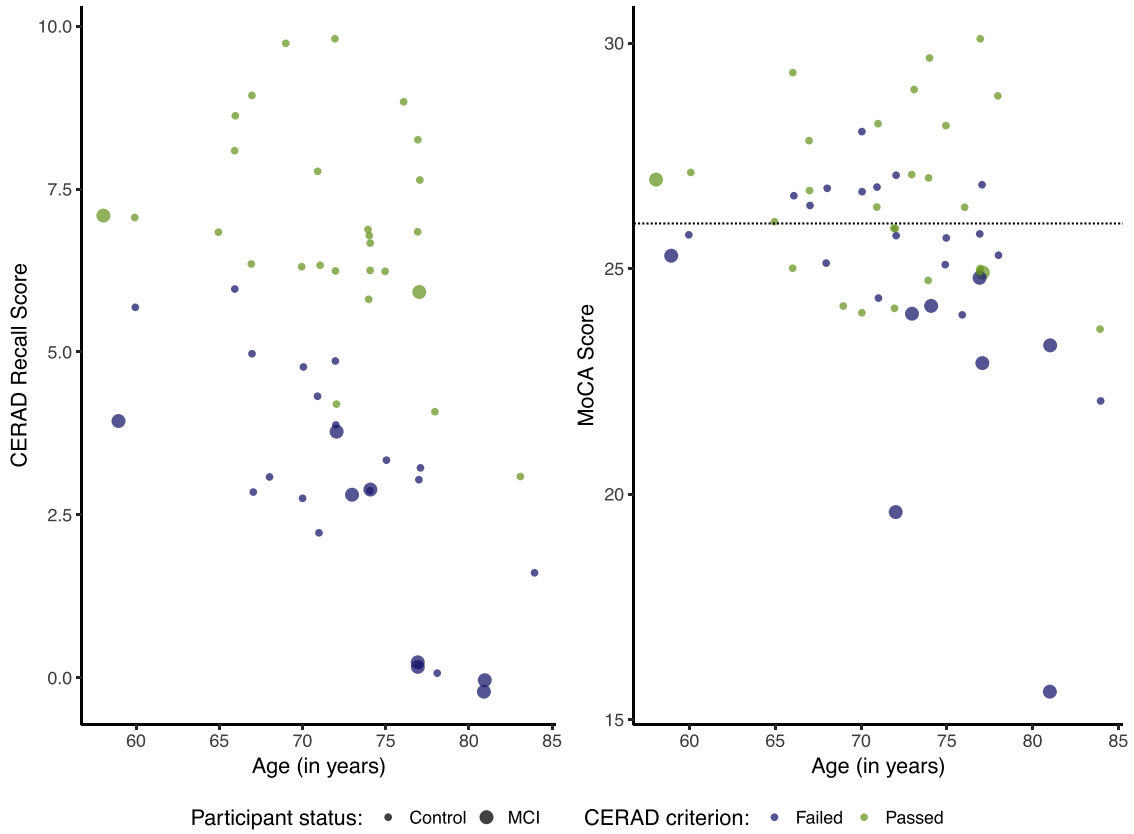

Fig. 3. The left panel plots the CERAD Word Recall score against age in years, with green circles depicting participants passing the CERAD threshold, and blue circles representing participants failing this threshold. Larger circles represent participants diagnosed with aMCI. The green smaller circles represent the $controls_{passed}$ subgroup, the blue smaller circles the $controls_{passed}$ subgroup. The right panel depicts the MoCA score as a function of age, with the dashed line representing the threshold. Data points for both panels are slightly jittered for presentation purposes.

age had a positive effect on CERAD score, whereas in the unaffected memory group increasing age is correlated with decreasing CERAD scores. Even though a number of explanations are possible for these patterns of results (e.g., selection effects for the affected groups and a standard age-memory decline effect for the healthy controls), any evidence for age having an effect on CERAD scores in the separate subgroups remained anecdotal (BFs < 2.13). However, the variance associated with the estimated durations is the measure of interest instead of the estimated duration itself, as the purpose of this part of the experiment is to estimate clock variability while excluding memory dynamics as much as possible. For this purpose, we assessed clock time variability based on the root mean squared residuals from a linear trend estimated per participant, a method outlined in Maaß and Van Rijn [18]. Fig. 4 depicts three violin plots, one for the participants diagnosed with aMCI, and one for both $controls_{failed}$ and $controls_{passed}$. As can be seen in these violin plots, each group contains a number of clearly outlying participants, but the majority of data is clustered around a Root Mean Square Residual (RMSR, a measure of variance, see Maaß and Van Rijn [18] for more details) of approximately .15. The barplot inset in Fig. 4 demonstrates that there is little effect of group on RMSR, with any qualitative trend suggesting that the participants classified as more memory affected show a smaller RMSR. However, we failed to find any evidence in favor of clock variance being influenced by memory status as a Bayesian linear regression analyses provided moderate evidence against RMSR being predicted by membership of either aMCI, $controls_{failed}$ or $controls_{passed}$ (BF = 5.56, ± 0.03%, with similar results when aMCIs are compared to all healthy controls, BF = 3.44, ± 0%). Adding age as covariate did not affect the pattern of results, as we again found moderate evidence against RMSR being predicted by group (BF = 5.67, ± 1.33%).

3.3. Multi-duration reproduction task

The data of the multi-duration reproduction task is graphically depicted in Fig. 5. The amnestic MCI group, depicted by the red line, shows the strongest central tendency, followed by the healthy controls that failed to reach the recall criterium of the CERAD ($controls_{failed}$, blue line). The healthy controls that passed the recall criterium of the CERAD ($controls_{passed}$, green line) demonstrate the smallest central tendency. For the analyses of these data, we centered both presented and reproduced duration by subtracting 1.4 s from the presented and reproduced durations. As a baseline model, we fitted a Bayesian linear effect model, with participant as random factor, predicting centered estimated duration by centered presented duration. Evidence in favor of this model was decisive when compared to a model just including an intercept (BF = 3.4×10^{862} ± 2.95%). Critically, comparing this model to a model that also included group as main effect and interaction term with presented duration (aMCI, $controls_{passed}$ and $controls_{failed}$) provided decisive evidence in favor of the more complex model (BF = 1.6×10^{14} ± 5.46%), providing evidence for the lines in Fig. 5 having different slopes. None of the tested additional models were preferred over the model including centered duration and group (i.e., decisive evidence against removing the interaction between group and duration: BF = 9.8×10^{14} ± 10.46%, against contrasting aMCI with all healthy controls BF = 119.46 ± 16.5%, and against adding age as predictor BF = 1.6×10^{5} ± 7.45%). To summarize, in a Bayesian model comparison the model in which the three different groups are associated with different central tendency effects was clearly preferred (the overall effect of centered duration is estimated at .66, with additional interactions with aMCI of -.18, with $controls_{failed}$ of .04, and with $controls_{passed}$ of .15).

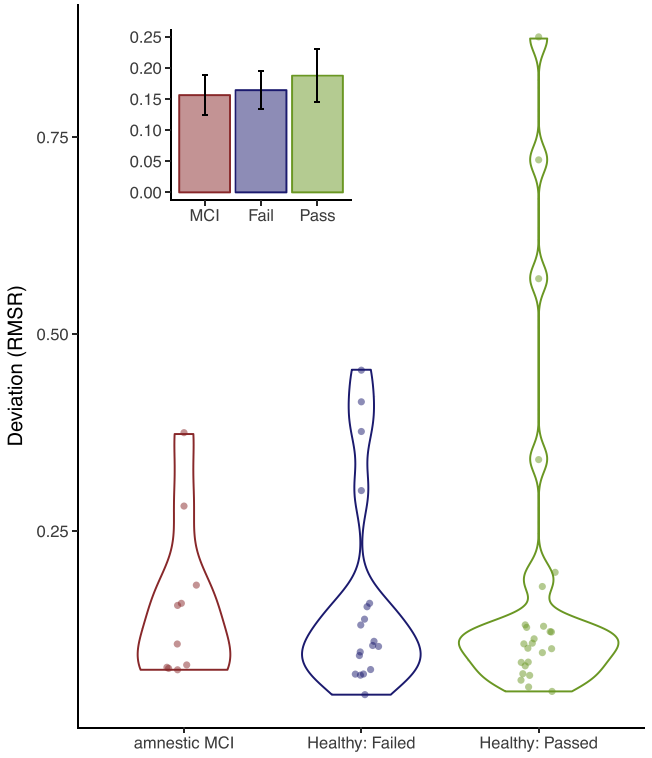

Fig. 4. Violin plots depicting observed deviation expressed in root mean square residuals from a linear fit estimated per participant, and the resulting continuous distribution plotted per participant group. Inset depicts mean deviation with error bars representing standard errors of the mean with the within-participants Cousineau-Morey correction applied.

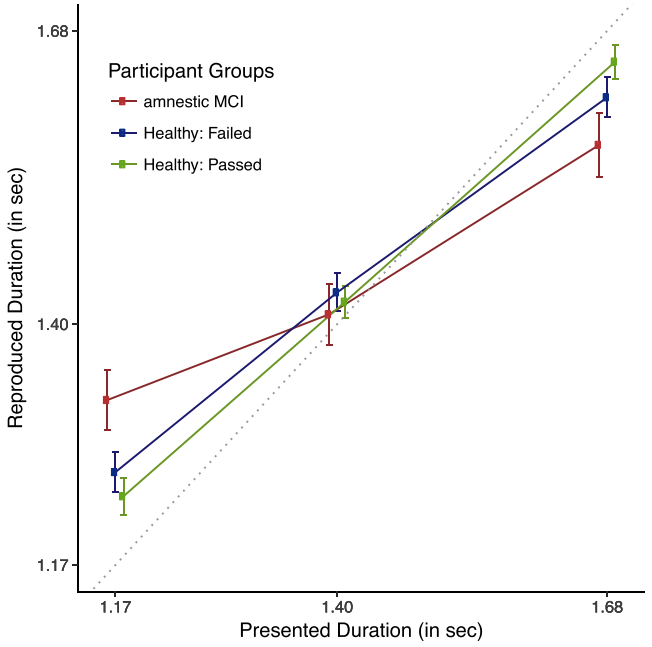

Fig. 5. Reproduced durations as a function of presented duration, plotted staggered on the horizontal axis and plotted separately for the three different participant groups. Error bars are standard errors of the mean with the within-participants Cousineau-Morey correction applied.

To assess the influence of clock variance on the amount of central tendency, we also added the RMSR to the preferred model. Decisive evidence was found against including it both as a main effect and in interaction between group (BF = 733.4 ± 2.39%), but moderate evidence was found in favor of adding it just as a main effect (BF = 3.30 ± 5.18%). Indeed, decisive evidence was obtained against an interaction between clock time variance and the different subpopulations (BF = 2962.5 ± 7.95) for the central tendency effect.

The above reported analyses assess the existing and strength of the central tendency effect per condition. However, these analyses do not take into account the previous durations. Given that the central tendency effect is assumed to be driven by the memory representations of the previous trials, one would expect that including the previously seen durations improves the model fit [14,51]. Indeed, extending the above-identified best fitting model with the reproduced duration associated with the previous trial, the two previous, and three previous trials was warranted (note that the first 3 trials of each block were excluded, $BF_{01} = 7.88 \times 10^{25} \pm 25.31\%$, $1.85 \times 10^{11} \pm 7.95\%$, $6.54 \times 10^{6} \pm 9.06\%$ respectively, BF are when compared to the most complex simpler model). Interestingly, the influence of these previous durations was modulated by participant group, as a model that includes interactions between the previous two durations and participant group was most likely given the data (BF_{01} for the interaction with just the previous duration: 56.24 ± 10.19%, with previous two durations: 6.41 ± 10.6%, with previous three durations: 0.0072 ± 10.83%, all compared to the most complex simpler model). Fig. 6 depicts the estimated weights for the previous trials for the three conditions. The order of the conditions is similar to the magnitude of the central tendency effect depicted in Fig. 5. These results suggest that the influence exerted by recent observations is a function of the level of memory dysfunction, but that the differential influence is reduced for later trials.

4. Discussion

This study addressed two main questions: First, we assessed whether clock variance, measured in a paradigm that minimizes the reliance on memory, is increased in an aged clinical population marked by memory deficits. The results suggest that neither age nor clinical status influenced clock time variability. Second, we assessed whether and how the memory deficiencies associated with aMCI affect in what way the current sensory experience and earlier experiences stored in memory are integrated. The results indicate that aMCI patients more strongly weigh prior experiences than healthy, age-matched controls, resulting in stronger central tendency effects. Interestingly, this pattern of results was also visible in the control sample, as splitting the healthy controls based on recall test scores revealed a similar pattern: the healthy controls with poorer memory performance displayed a stronger reliance on previous presented durations than the controls with better memory

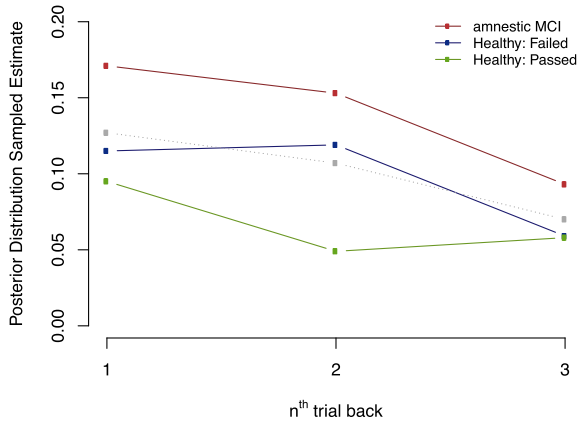

Fig. 6. Linear-mixed effect model-based estimate of the influence of the previous trial's reproduced duration on the current duration (as conceptualized by the posterior distribution sampled estimates) per participant group. Grey dashed line depicts the main effect when group effects are not taken into account, the colored lines depict the three participant groups.

performance. As the temporal production variability was similar among all groups, these effects cannot be easily explained by higher clock variance.

The observed evidence against clinical status determining clock variance contrasts earlier reports in which populations characterized by cognitive decline (ranging from decline present in healthy aging to neurodegenerative diseases) have been associated with increased clock variance (e.g. [23–29]). Interestingly, we also found no evidence for increased clock variance as a function of age in our sample of 58 to 84 year old participants. One potential explanation is that the majority of the earlier studies have assessed clock variance utilizing bisection tasks or discrimination tasks (e.g [24,37,52]). These tasks require accurate memory functioning and comparison mechanisms: either for the comparison of the two extreme durations in the case of the bisection paradigm, or for encoding and retrieving the standard duration in discrimination tasks. These studies potentially confound processes related to memory functioning with clock variance, making it difficult to distinguish whether variances in observed accuracy are due to increased clock variance or deficient memory functions. The importance of memory updating during temporal production tasks is evident when comparing two separate studies that either presented or withheld feedback during a temporal reproduction task. Wild-Wall et al. [28] asked participants to repeatedly produce a 1.2 s duration and encouraged participants to use feedback for improving temporal response accuracy. Their results provided evidence in favor of a decline in temporal performance in an aged population. On the other hand, when Rammsayer [53] asked participants to repeatedly produce a 1 s duration without feedback, age did not affect performance, suggesting that age affects the processing or encoding of the feedback, instead of the clock. We therefore propose that clock variability, especially in clinical populations associated with (amnesic) cognitive decline, should be assessed using paradigms devoid of memory components (e.g., learning standard durations, incorporating feedback, etc.).

The observed negative correlation between the magnitude of the central tendency effect and memory functioning might be considered paradoxical as it implies that with *decreasing* memory functioning, the prior - which can be seen as the memory for previously perceived stimuli - has *stronger* influence on subsequent performance. Interestingly, the increased effect was also observable when splitting the healthy controls by memory recall test score, with those having failed the memory recall test displaying a greater central tendency effect. The central tendency effect can be observed in a multifold of perceptual processes encompassing the judgment of quantities. It is a flexible process in which, depending on the noisiness of the sensory input, prior knowledge is integrated to improve performance in conditions where perceived estimates are imprecise. This can be captured in Bayesian inference by assuming that with a broader likelihood (i.e., noisy sensory input), more weight is given to the prior (see Fig. 1). This interplay leads to a trade-off between accuracy and reliability. Our previous research has shown that in young healthy adults the clock variance, and thus noisiness of the sensory input, derived from a 1-second production task predicts the strength of central tendency in a multi-duration reproduction task, with higher variance leading to larger influence of the prior durations [18]. However, given the hypothesized role of the memory system in multi-duration reproduction tasks and the specific populations tested, we expected notable effects of memory status, and either no or relatively small effects of clock noise on central tendency magnitude. Indeed, the magnitude of the observed central tendency differed for the three groups of participants, whereas no relation was observed between clock noise and central tendency measures. This implies that the strong central tendency effect observed in memory impaired individuals is driven by processes specifically related to memory functioning in either the temporary (working) memory or long-term (reference) memory. Impairment of the latter would mean that durations are not stored in reference memory. Because reference memory is essential for the development of a prior, impairment of the reference memory system should lead to smaller or non-existent central tendency effects. Our data clearly show central tendency effects in aMCI individuals, meaning that they develop a prior and thus intact long-term storage. Moreover, the individual traces of earlier presented durations must also be intact as in addition to an overall central tendency effect, there is a noted influence of previous trials on the current trial, an effect especially pronounced in the aMCI individuals (see Fig. 6). Yet, these results suggest that the representation in short term memory exerts less influence on the reproduced durations in memory affected groups, which might be caused by losing reference to the most recently perceived duration (cf., [54,55]). Due to this impoverished access to the representation, the earlier stored traces will exert a stronger effect, resulting in a stronger central tendency effect. Note that this explanation requires a more refined representation of the recent experiences than is accounted for in Bayesian Observer Models that model the prior by a single distribution (e.g. [36,37],). However, earlier work (e.g. [56,57],) has demonstrated that Kalman-filter based models can account for similar effects as the summary models (see also [14,51]) while retaining access to recently observed durations. These models can therefore be extended to account for the proposed effects.

In terms of the rationale depicted in Fig. 1, this would not so much suggest a change in the width of either the likelihood or prior distributions, but instead a different, lower weighing of the relative contribution of the likelihood as a function of memory deficiencies. This could be implemented by assuming a multiplication factor scaling the distributions for the likelihood, with values smaller than 1 indicating a reduced contribution of the stimulus-driven likelihood. In principle, it should be possible to fit the Bayesian model to the performance of individual participants, and derive indices for this scaling factor, the precision of the likelihood, and of the prior. However, even though these indices carry different theoretical interpretations, their behavioral signature is largely identical: an increased central tendency effect with only subtle differences associated with each index. It will therefore be necessary to validate this modeling approach by constraining or cross-validating the model on the basis of additional data, for example a precise behavioral memory index (e.g., [58]), neurobiological markers of memory (dys) function or deficiencies such as Tau pathology [59], and measures of clock variability such as the 1-second production task [18].

Another potential neurobiological marker is acetylcholine (ACh) as neurophysiological studies in animals have demonstrated that decreased ACh levels are correlated with decreased thalamocortical synaptic transmission, relative to intracortical synaptic transmission (for a review, see [60]). As thalamocortical connections drive stimulus-driven processing, lower ACh levels reduce the influence of incoming sensory information [61]. Even though existing studies have primarily focused on the transmission of information of visual or auditory nature, the thalamocortical link suggests that this information has already been processed by the earlier sensory processing, suggesting that the influence of temporal percepts is also affected by ACh levels. Interestingly, ACh levels are reduced in Alzheimer and MCI, and correlate with the severity of clinical symptoms [62]. Taken together, these results suggest that ACh levels directly map onto the relative weighing of the likelihood over the prior, explaining the stronger central tendency effects.

In sum, we demonstrate that the central tendency effects observed in an interval timing task correlate with the severity of memory dysfunctions in a pre-clinical and a healthy aged sample. As the reproduction task is easy to administer and be administered repeatedly without learning effects, this task could potentially be a useful measure of memory functioning, especially addressing the efficacy of the thalamocortical connections in behavior guided by incoming information.

4.1. Conclusion

To conclude, we have presented a method to disentangle the influence of noise in temporal resolution from memory functioning in timing behaviors by assessing clock variance and memory-driven

central tendency effects with two separate tasks. We have shown that the clock variance does not increase as a function of memory impairment in aMCI individuals compared to healthy aged participants. Instead, we found that the amount of central tendency is driven by memory impairment. This suggests that in this population the central tendency process is not used as a heuristic to compensate for a lack of accuracy, but that a loss of the individual trace of the current interval leads to an estimate that is heavily influenced by the prior. We therefore conclude that short-term memory is the affected component in clinical populations with memory deficits, as the results are best explained by the assumption that these subpopulations have difficulty keeping the current interval available. As these effects are already observable in participants who score lower on traditional memory tests, but have not been diagnosed as aMCI, the reproduction task has the potential to serve as a continuous measure of memory performance, in both clinical and pre-clinical populations.

Funding

This research has been supported by the research program “Interval Timing in the Real World: A functional, computational and neuroscience approach” (project number 453-16-005) financed by the Netherlands Organization for Scientific Research (NWO) awarded to Van Rijn.

Declaration of Competing Interest

The authors have no competing interests to declare.

Acknowledgements

We thank Wenzel Glanz (Neurologist, DZNE Magdeburg) and his staff for the help in recruiting aMCI patients and Leendert van Maanen for fruitful discussions.

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