Contextual novelty detection and novelty-related memory enhancement in amnestic Mild Cognitive Impairment

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Introduction: Though novelty processing plays a critical role in memory function, little is known about how it influences learning in memory-impaired populations, such as amnestic Mild Cognitive Impairment (aMCI).

Methods: 21 aMCI patients and 22 age- and education-matched healthy older participants performed two tasks— (i) an oddball paradigm where fractals that were often repeated (60% of the stimuli), less frequently repeated (20%), or novel (presented once each) were shown to assess novelty preference (longer viewing time for novel than familiar stimuli), and (ii) a Von Restorff paradigm assessing novelty-related effects on memory. Participants studied 22 lists of 10 words. Among these lists, 18 contained an isolated word different from the others by its distinctive aspect, here the font size (90-point, 120-point or 150-point against 60-point for non-isolated words). The remaining four were control lists without isolated words. After studying each list, participants freely recalled the maximum words possible.

Results: For the oddball task, a group-by-stimulus type ANOVA on median viewing times revealed a significant effect of stimulus type, but not of group. Both groups spent more time on novel stimuli. For the Von Restorff task, both aMCI and healthy controls recalled the isolated words (presented in 120-point or 150-point, but not 90-point) better than others (excluding primacy and recency effects). Novelty-related memory benefit—gain factor—was computed as the difference between the recall scores for isolated and other words. A group-by-font size ANOVA on gain factors revealed no group effect, nor interaction, suggesting that aMCI patients benefited from novelty, alike controls.

Conclusion: Novelty preference and the boosting effect of isolation-related novelty on subsequent recall seem preserved despite impaired episodic memory in aMCI patients. This is discussed in the light of contemporary divergent theories regarding the relationship between novelty and memory, as either being independent or parts of a continuum.

Keywords: novelty; episodic memory; mild cognitive impairment

Introduction

Individuals with amnestic Mild Cognitive Impairment (aMCI) are considered at risk of developing Alzheimer's disease, with 50 to 80% of them progressing to dementia in subsequent years (Petersen et al., 2009). In memory clinics, they present with complaints of changes in their memory abilities, and neuropsychological testing reveals an objective memory decline, that can sometimes be accompanied by other cognitive deficits (e.g., executive functions, language), despite a relatively preserved autonomy in everyday life (Albert et al., 2011).

Novelty is a concept closely related to memory. Indeed, something is considered as novel if it has not been encountered before and is unknown. Moreover, novelty can promote learning of new information (Schomaker & Meeter, 2015). In the context of aMCI and dementia, the study of novelty-related processes is important to better characterize the memory profile of these patients by determining whether impaired novelty processing is an early cognitive deficit or alternatively can contribute to improve memory performance. Little research has been dedicated to novelty processing in aMCI (for a review, Bastin et al., 2019) and firm conclusions cannot be drawn given the paucity of studies and the variety of methods used. The latter is a key element as there are different types of novelty that are supposed to depend on distinct neural mechanisms (Kafkas & Montaldi, 2018).

Two studies assessed whether aMCI patients' attention is attracted to novel stimuli using the visual paired comparison task (Crutcher et al., 2009; Nie et al., 2020). In this task, participants are first presented with two identical pictures side-by-side, then see a pair of pictures, the previously presented one and a new one. The measure is the time spent looking at the new picture compared to the old one. Crutcher et al. (2009) compared the percentage of time spent on the novel picture between a group of 6 aMCI patients and 15 controls under 2 conditions manipulating the delay between the study and test trials. When the delay is 2 seconds, aMCI patients had a normal novelty-detection behaviour, spending more of the test trial looking at the novel picture than the old one. But when the delay was 2 minutes, aMCI patients looked significantly less the novel picture compared to controls. Using the same paradigm as Crutcher et al. (2009), Nie et al. (2020) observed an overall decreased preference for novelty in a larger group of aMCI patients, but did not compare the two delays, so that we do not know whether this group of patients had preserved novelty detection when they did not have to rely on long-term memory. Although these studies suggest an alteration of novelty detection in aMCI patients, it is important to note that they concern exclusively one type of novelty called *stimulus novelty* or *absolute novelty* (Bastin et al., 2019). Indeed, they do not provide information about the possible preservation of other types of novelty such as *contextual* or *associative novelty*.

Yet, contextual novelty can enhance memory. For example, in memory tasks, a novelty-related memory enhancing effect can be observed when novel materials are presented alongside familiar materials during the encoding phase (Tulving & Kroll, 1995). In one study, aMCI patients and controls studied previously well-known words or melodies mixed with novel ones (i.e., novel pseudowords or unknown melodies), and then performed a yes/no recognition memory task. The experiment failed to demonstrate novelty-related boosting effect; recognition memory performance was better for well-known than novel stimuli. This suggests that prior knowledge is a more powerful facilitator of encoding in episodic memory than novelty, at least in this kind of paradigm (Bird et al., 2011; Jonin et al., 2022). Moreover, aMCI patients had worse recognition performance than controls for familiar items, but not for novel items.

Another approach to investigate novelty-related memory effects consists in assessing the primacy effect in list recall. According to Davelaar (2013), the better recall of the first two or three items of a list compared to the middle items is due to their distinctive status arising from the change in episodic context representations, thereby creating contextual novelty. Studies examining serial position effects in free recall in MCI reported mixed results, with some work indicating that the serial position curve is preserved despite an overall decrease of recall performance (Bennett et al., 2006; Moser et al., 2014) and other work showing a diminished primacy effect relative to recency effect in these patients (Cunha et al., 2012; Howieson et al., 2011).

Given the lack of studies on novelty processing in aMCI, the current experiment aimed at investigating whether aMCI patients demonstrate intact preference for novelty and improvement of memory performance for novel stimuli by using two paradigms that have been used in various populations to assess contextual novelty processing, but never in aMCI (Bastin et al., 2019; Schomaker & Meeter, 2015): an oddball task (inspired by Daffner et al., 2007) and a Von Restorff task (inspired by Vitali et al., 2006). On the one hand, in oddball paradigms, subjects are typically presented three types of stimuli in a random sequence: a stimulus is repeated on a majority of the trials (generally 60 or 80%), a stimulus is repeated infrequently (the "oddball", often 10% to 20% of the trials) and novel stimuli appear only once (10% to 20% of the stimuli). Considering the reaction to novelty, this paradigm typically induces an attentional orientation towards novel stimuli that is evidenced by longer viewing time of novel stimuli compared to repeated ones (Daffner et al., 2007). On the other hand, the Von Restorff task allows the evaluation of novelty-related memory effects. The fundamental principle of this paradigm is the presentation of a list of items to be memorized, including one or more items with a distinctive characteristic (e.g., font size, colour, semantic category, etc.). This deviant item is commonly regarded as novel and has been shown to have a beneficial impact on memory (Hunt, 1995)—i.e., it is generally better recalled.

Materials and methods

Participants

This study was conducted in accordance with the ethical guidelines described in the Declaration of Helsinki (1964) and received approval from the local Ethics Committee (#2012/274). The sample size was estimated a priori by means of the G*Power 3.1 software (Faul et al., 2007). To be able to detect small size effects (f = .20) with a statistical power of .80 and an α threshold of .05 on a 2 groups-by-3 repeated measures ANOVA, the recommended sample size was 42 participants in total.

Twenty-one patients diagnosed with an aMCI were recruited from the Memory Clinic of Liege (sex: 12 women). The diagnosis relied on the criteria for aMCI from the Mayo Clinic (Petersen & Negash, 2008). Patients were selected based on general examination, neurological and neuropsychological assessments, and laboratory evaluation. The patients demonstrated both subjective and objective memory decline. They did not experience difficulties in their daily activities and they did not fulfil the criteria for dementia. The control group was composed of 22 healthy older participants (14 women). Table 1 summarizes the mean demographic and clinical data for the two groups. The two groups did not differ significantly in terms of age, $t(41) = .46$, $p = .64$, $d = .14$ (Cohen's d for t-tests' effect size), or education, $t(41) = -1.46$, $p = .15$, $d = .45$. Healthy volunteers had no previous psychiatric or neurological disorders and were not under the influence of any psychotropic medication. All the participants were French-speakers. After being informed of the terms of the study and providing their written informed consent, participants took part to two sessions, with a delay of less than 7 days between the sessions. The first session consisted of a neuropsychological evaluation. The second was dedicated to the two experimental tasks (for which the material is available at https://osf.io/8dnpc/?view_only=205c289ee3d343b2856d2201676c9633).

Table 1. Averaged demographic data, MMSE scores, and performance to the Free and Cued Selective Reminding Test for both groups.

		aMCI	**Control**
		mean ± *SD*	*mean* ± *SD*
	Age (years)	69.9 ± 7.1	68.9 ± 7.0
	Education level (years)	13.7 ± 3.3	12.3 ± 3.1
	Sex (F/M)	9/12	14/8
	MMSE score (/30)	26.9 ± 2.3	28.9 ± 1.0
Free and Cued Selective Reminding Test	Immediate recall (/16)	14.5 ± 1.9	15.9 ± 0.3
	Free recall 1 (/16)	5.8 ± 2.3	9.6 ± 2.2
	Total recall 1 (/16)	12.6 ± 2.7	15.3 ± 1.2
	Free recall 2 (/16)	7.4 ± 3.3	10.9 ± 2.2
	Total recall 2 (/16)	14.0 ± 2.1	15.3 ± 0.9
	Free recall 3 (/16)	7.1 ± 2.8	12.0 ± 2.3
	Total recall 3 (/16)	13.8 ± 2.3	15.8 ± 0.5
	Delayed free recall (/16)	7.5 ± 4.4	12.6 ± 2.0
	Delayed total recall (/16)	13.4 ± 3.1	15.9 ± 0.2
	Recognition hits (/16)	15.1 ± 1.2 (9 NaN)	15.9 ± 0.2

Neuropsychological evaluation

Each participant performed five neuropsychological tests: the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), the Free and Cued Selective Reminding Test (Grober & Buschke, 1987), the Stroop test (GREFEX, 2001; Stroop, 1935), the semantic (animals, fruit) and phonemic (“T”, “N”, and “P”) verbal fluency tests (St-Hilaire et al., 2016), and the Digit Span subtest of the Wechsler Adult Intelligence Scale-IV (WAIS-IV).

Patients with aMCI were only included in the study if they had at least one pathological score on the Free and Cued Selective Reminding Test. In contrast, control participants were included if they performed within norms on all scores of this same test and had a score above 26 on the MMSE. Patients who have been diagnosed with aMCI had MMSE score between 23 and 30 (mean = 26.86 ± 2.29), while control participants had MMSE score between 26 and 30 (mean = 28.86 ± 1.04). Participants’ individual scores to the MMSE and the Free and Cued Selective Reminding Test are available in Appendices 1 (for controls) and 2 (for aMCI patients).

Experimental tasks

The tasks are described below in the order in which they were administered to participants. For the entire session, participants sat comfortably in a quiet room about 50 cm from the laptop screen on which stimuli appeared. Stimulus presentation and response collection were performed using the OpenSesame software (version 3.2.8; Mathôt et al. 2012). The experiments were displayed at a resolution of 1024*768 px.

An adaptation of the oddball paradigm (inspired by Daffner et al., 2007)

Our oddball-like task was divided into five blocks. Each block consisted of 27 stimuli including the same stimulus repeated 17 times (called "standard" –64% frequency), 5 new stimuli presented only once each (called "new" –18% of the block stimuli) and another stimulus repeated five times (called "target" –18% frequency). Stimuli were 4 x 4 cm square coloured abstracts patterns (examples in Figure 1B) that appeared in the centre of the screen on a grey background. Participants were asked to look at the pictures as long as they wanted and to press the space key of the laptop keyboard when they wanted to move on to the next stimulus. Participants were told explicitly that there would be no memory test on the pictures at the end of the experiment. The viewing time of each image (VTs) was recorded in milliseconds. Before the appearance of each stimulus, a fixation cross appeared in the middle on the screen for a duration of 495ms. The course of the task is shown in Figure 1. Between blocks, participants had the possibility to take a break if required.

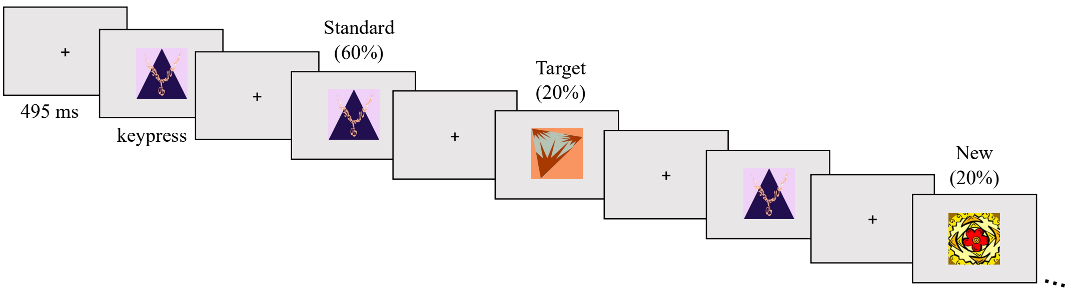

Figure 1. Illustration of the fractals presented during our modified version of the oddball task.

An adaptation of the Von Restorff paradigm (inspired by Vitali et al., 2006)

In our study, the paradigm was composed of 22 French word-lists. Each list contained 10 common words. We verified that, for the 18 lists containing a target word, the lexical frequency of target and non-target words were equivalent ($t(178) = -.43$, $p = .67$)—i.e., the frequency of occurrence per million of words in books according to the French Lexicon project (Ferrand et al., 2010) available on Lexique 3.83 website. Following pilot work to set up the procedure, each word appeared on the screen for 1000ms. All words appeared in a black font on a grey background. Before each word, a fixation cross appeared during 1000ms. Among these 22 word-lists, 18 contained nine non-target words presented in 60-point font and one isolated word presented in a bigger size font (either 90-point, 120-point or 150-point font: 6 lists per font size condition). The isolated word appeared evenly between the 4th and the 7th position in order to avoid confusion with primacy and recency effects (see Figure 2 for an illustration of the task flow). Participants were not informed that some words would appear in a bigger font size. The remaining four lists were control lists that contained only non-target words of the same 60-point font. The different types of lists were mixed so that there was no succession of the same type.

After the presentation of each list, a green background appeared for 7 seconds. Participants were asked to wait and to mentally repeat words. After this delay, there was a free recall phase in which participants had to recall orally as many words as possible. As soon as they had finished for one list, they had the possibility to press a button to begin the next list or to make a pause if needed. For each list, the experimenter wrote down the words that were recalled. Before completing the task, participants practiced a training list without any target word in order to get used to the way items were presented and to familiarize themselves with the instructions.

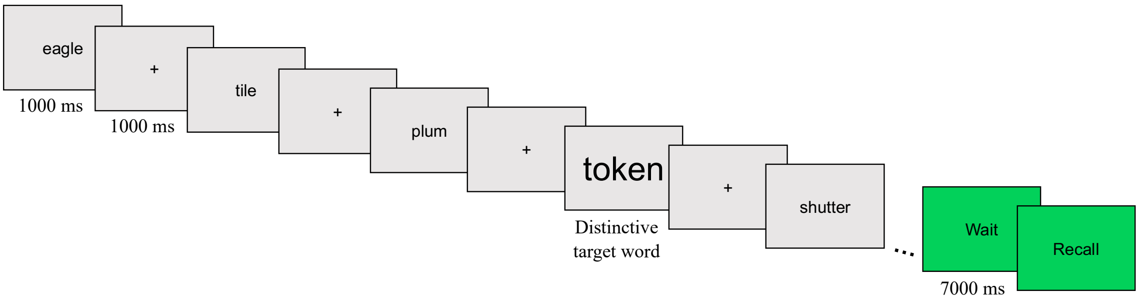

Figure 2. Illustration of a target word (i.e., "token") among non-target words in a list of our modified version of the Von Restorff task.

Data analysis

All statistical analyses were performed with JASP (Version 0.17.1). The threshold of significance α was .05. The graphs were generated with either JASP or the Seaborn Python 3 library.

Oddball paradigm

One aMCI patient and two control participants (anonymized codes of discarded participants: Control 1, Control 6, and aMCI 5) were excluded from the analyses for the oddball task because they were considered outliers (i.e., their performance differed by more than 2 standard deviations from the average of their respective groups, as their VTs were abnormally long). For this task, the analyses were therefore conducted on the remaining participants (control group: n = 20; aMCI group: n = 20).

The first presentation of the target and the standard stimulus of each block were discarded from the analyses because, seen for the first time, they were novel and not yet treated as familiar. The median VTs for each condition (standard, target, and new), collapsed across the blocks, were calculated. The median VTs were entered into a mixed ANOVA with condition (standard, target and new) as within-participant factor and group (control or aMCI) as categorical factor. In each group, we then used planned comparisons to test our hypothesis that new stimuli lead to longer VTs than standard and target stimuli. A Bonferroni correction was applied to account for the number of comparisons.

Since previous mixed findings (see Introduction) lead us to consider the possibility that aMCI patients would have preserved novelty-related processes, we expected the null hypothesis (i.e., the ANOVA to not reveal differences between groups) to be a finding of interest. To investigate such an absence of group effect, we also computed the Bayesian version of the repeated measures ANOVA. Unlike the frequentist approach, which only rejects the null hypothesis without otherwise bringing evidence in its favour, the Bayesian method quantifies how much evidence there is toward a specific hypothesis: either the null hypothesis, or the alternative one (Quintana & Williams, 2018). We calculated the Bayes Factor (BF_{10}) in comparison to the null model for the following models: group, condition, and their interaction. The BF_{10} value represents how many times a model is more or less likely to explain the data with respect to the null model (Quintana & Williams, 2018): values below 1 indicates evidence in favour of the null model while values above 1 indicates evidence in favour of the alternative hypothesis. As rule of thumb (Quintana & Williams, 2018), values between 3 and 10 or between .33 and .10 are interpreted as moderate evidence for the alternative model and the null model respectively, while values above 10 or below .10 are considered as strong evidence for the alternative model and the null model respectively. Values between .33 and 3 represents only anecdotical evidence.

Then, to investigate the relationship between episodic memory impairment and novelty preference, we computed the correlation between, on the one hand, the sum of the words recalled during the three free recall of the Free and Cued Selective Reminding Test (/48) and on the other hand, the intensity of novelty preference on the oddball task—i.e., the median VTs for novel stimuli divided by the median VTs for familiar standard stimuli. Since the normality of this last variable was violated according to Shapiro-Wilk test, we used Spearman's correlations. Correlations were computed separately for aMCI patients and healthy controls.

Von Restorff paradigm

First, the percentages of correctly recalled non-target words were calculated for the first 3 positions (primacy effect), the last 3 positions (recency effect) and positions 4 to 7 (middle) across all lists (Cunha et al., 2012). The percentages were submitted to t-tests to compare primacy and recency effects between groups. Bonferroni corrections were applied to correct α for multiple tests.

Then, novelty-related analyses focused on the middle position in order to eliminate the influence of primacy and recency effects. For the 18 lists containing an isolated word, we calculated the percentage of correctly recalled isolated words. The percentage of non-target words from the 18 lists containing an isolated word was compared to the percentage of non-target words from the 4 lists that did not contain an isolated word. As these percentages did not differ significantly, $F(1, 41) = 0.34$, $p = .56$, $\eta^2_p = .008$, there were collapsed for the comparison with recall of isolated words. The memory benefit due to novelty was computed as the difference between the percentage of recalled isolated words of each font size (i.e., isolated words in 90-, 120-, or 150-point) and the percentage of recalled non-target words. This score, called gain factor (GF), was submitted to a 2 groups (aMCI, controls) by 3 font sizes (90, 120, 150) mixed ANOVA. For the same reasons as mentioned earlier, the Bayesian version of the repeated measures ANOVA was computed and BF_{10} are reported.

Finally, to determine whether there was a significant improvement of recall performance for the isolated words compared to the non-target words, the percentage of recalled isolated words of each font size (i.e., isolated words in 90-, 120-, or 150-point) was compared to the percentage of recalled non-target words in each group by means of dependent-sample t-tests.

To investigate the relationship between episodic memory impairment and the boosting effect of isolation-related novelty on subsequent recall, we computed the correlation between, on the one hand, the sum of the words recalled during the three free recalls of the Free and Cued Selective Reminding Test and on the other hand, the GF of the Von Restorff paradigm. Since both variables were normally distributed according to the non-significant Shapiro-Wilk tests, we used Pearson's correlations. Correlations were computed separately for aMCI patients and healthy controls.

Results

Oddball paradigm

Median VTs per group and per condition are shown in Figure 3 (for boxplots with individual median VTs, see Appendices 3). Note that sphericity was violated according to Mauchly's test ($W = .40$; $p < .001$) and that the Greenhouse-Geisser correction was applied ($\varepsilon = .625$). The condition (standard, target and new) by group (control or aMCI) mixed ANOVA on median VTs showed that the main effect of group was not significant, $F(1,38) = 2.72$, $p = .11$, $\eta^2_p = .07$, but there was a large and significant main effect of condition, $F(2,76) = 19.99$, $p < .001$, $\eta^2_p = .35$. The interaction between condition and group did not reach significance, $F(2,76) = .11$, $p = .80$, $\eta^2_p = .003$. The Bayesian version of the ANOVA confirmed the effect of the condition with decisive strong evidence ($BF_{10} = 164550.54$), and indicates moderate evidence against an interaction condition*group ($BF_{10} = .15$). However, the Bayesian analysis did not reveal either an effect or an absence of effect for the group ($BF_{10} = 1.002$).

In both groups, planned comparisons exploring the effect of condition showed longer VTs for new than standard stimuli (control: $p < .001$; aMCI: $p < .001$) as well as for new compared to target stimuli (control: $p = .001$; aMCI: $p = .007$). However, VTs did not differ significantly between standard and target stimuli (control: $p = .26$; aMCI: $p = .18$).

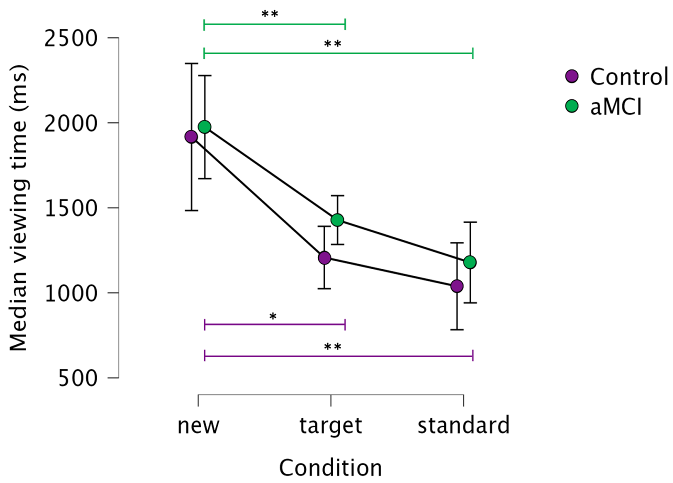

*Figure 3. Oddball paradigm: Median VTs (in ms) by condition (new, target and standard) for control participants and aMCI patients with confidence interval of 95%. Asterisks show the significant differences according to planned comparisons. *p<.05; **p<.001*

Spearman's correlations analyses did not show any significant relation between novelty preference and episodic memory performance in controls, $r(18) = .01$; $p = .98$, 95% CI [-.44, .45]. There was a tendency for a positive correlation in aMCI patients, $r(18) = .45$; $p =.05$, 95% CI [.005, .74]. The scatter plots are available in Appendices 5.

Von Restorff paradigm

As expected, the total percentage of recalled words (TOT%) was significantly higher in the control than in the aMCI group, $t(41) = 4.58$, $p < .001$, $d = 1.40$. The t-tests also showed a significant difference in primacy effect between groups, $t(41) = 4.22$, $p < .001$, $d = 1.29$ (i.e., greater primacy effect in controls) while there was no significant difference in recency effect between groups, $t(41) = 1.52$, $p = .14$, $d = .46$. See Table 2 for means and SD values.

Table 2. Averaged percentage of words recalled per group for all the words (TOT%), for the three first (primacy effect) and three last (recency effect) words of each list.

	aMCI	**Control**
	mean ± *SD*	*mean* ± *SD*
Primacy effect (%)	33.4 ± 16.8	52.7 ± 13.0
Recency effect (%)	37.8 ± 17.8	46.1 ± 18.4
TOT%	31.4 ± 9.1	43.1 ± 7.5

The group-by-font size ANOVA on GF showed a significant main effect of font size, $F(2,82) = 17.72$, $p < .001$, $\eta^2_p = .30$ (see Figure 4 for group plots and Appendices 4 for more detailed boxplots). The main effect of group was not significant, $F(1,41) = .10$, $p = .76$, $\eta^2_p = .002$, nor was the interaction between variables, $F(2,82) = 1.79$, $p = .17$, $\eta^2_p = .04$. See Table 3 for means and SD values. Interestingly, the Bayesian version of the ANOVA revealed moderate evidence in favour of an absence of effect of the group ($BF_{10} = .29$) and support our findings. The Bayesian analysis highlighted strong decisive evidence in favour of an effect of the font size ($BF_{10} = 46997.97$) too, and anecdotical evidence in favour of the absence of group*font size interaction ($BF_{10} = .51$).

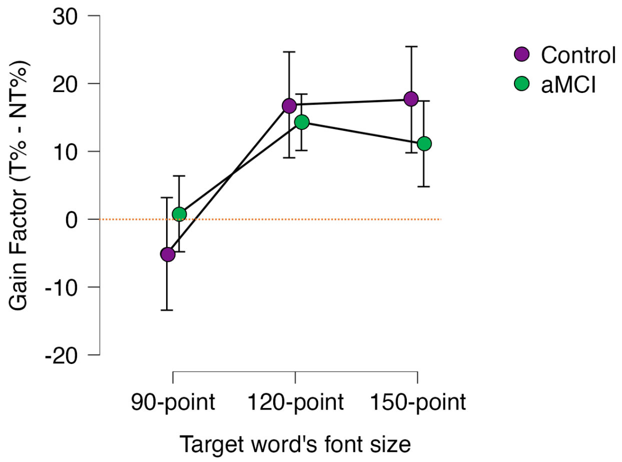

Figure 4. Von Restorff paradigm: Average Gain Factor (in %) by condition (90-, 120- or 150-point) for control participants and aMCI patients with confidence interval of 95%. The orange dotted line indicates null GF% and represents the level of no novelty gain.

In controls, when the target word was presented in 90-point font size, the difference between recall of target words (T%) and recall of non-target words (NT%) did not reach significance, $t(21) = -1.02$, $p = .32$, $d = -.22$ while the analyses showed a significant difference between T% and NT% in the two other conditions (i.e., 120- and 150- point), $t(21) = 5.48$, $p = < .001$, $d = 1.17$ and $t(21) = 3.81$, $p = .001$, $d = .81$ respectively. The same pattern of results was highlighted in aMCI patients: for 90-point, $t(20) = -.21$, $p = .84$, $d = .05$; for 120-point, $t(20) = 4.06$, $p = <.001$, $d = .89$; for 150-point, $t(20) = 2.83$, $p = .01$, $d = .62$.

Regarding the relation between episodic memory performance and the boosting effect of novelty on subsequent recall, the correlation between the gain factor on the Von Restorff task and the free recall memory performance on the Free and Cued Selective Reminding Test was not significant, neither in the control group ($r(20) = -.40$, $p = .06$, 95% CI [-.71, .02]), nor in the aMCI group ($r(19) = .11$, $p = .65$, 95% CI [-.34, .51]). Nevertheless, the tendency towards a negative relation, which was observed in controls, seemed absent in the aMCI group. The scatter plots are available in Appendices 6.

Table 3. Averaged percentages of words recalled per group for each type of list depending on target word's font size.

Font size	Performance	aMCI	Control
90-point	*T%*	24.6 ± 22.1	27.3 ± 22.7
	NT%	15.6 ± 8.9	30.6 ± 12.3
	GF	0.8 ± 22.7	-5.1 ± 19.9
120-point	*T%*	38.1 ± 17.6	49.2 ± 15.8
	NT%	28.3 ± 13.5	31.3 ± 9.9
	GF	14.3 ± 15.8	16.8 ± 15.9
150-point	*T%*	34.9 ± 18.2	50.0 ± 21.2
	NT%	25.7 ± 13.5	31.8 ± 10.2
	GF	11.1 ± 18.5	17.6 ± 21.7

GF: gain factor representing the memory benefit of the novelty; T%: percentage of target words correctly recalled; NT%: percentage of non-target words correctly recalled

Discussion

Novelty-related processes remain understudied in the context of aMCI (Bastin et al., 2019). Yet, given its close relationship with memory processes, novelty processing is a crucial aspect to better understand the cognitive profile of these patients but also the models of memory impairment in this population. Since contextual novelty can boost memory performance (Klever et al., 2021; Lorents et al., 2023; Schomaker, 2019), our study investigated whether aMCI patients show preserved novelty preference for context-induced novelty and whether their memory performance can benefit from isolation-related novelty—i.e., a type of contextual novelty, or alternatively whether novelty-related effects are impaired in these patients.

Novelty detection was assessed using an oddball paradigm inspired by Daffner et al. (2007). Unlike Daffner et al. (2001) who demonstrated that patients diagnosed with probable Alzheimer's disease (mean MMSE score = 24 ± 1) distributed their viewing time evenly between new and familiar stimuli (i.e., reduced preference for novelty) unlike controls, our results did not show any significant difference between control participants and aMCI patients (mean MMSE score = 26.9 ± 2.3). Participants from both groups spent more time looking at new stimuli compared to familiar (low- and high-frequency) ones. The preference for novelty, specifically contextual novelty as evaluated here, seems preserved in aMCI patients since their pattern of viewing time, except that it was globally longer, resembled the one of the control participants. Note that given the lack of evidence provided by the Bayesian analysis, we might be in an underpowered analysis situation and cannot firmly rule out a potential effect of the group for this task.

To examine novelty-related memory benefit, we used a Von Restorff paradigm (Von Restorff, 1933) inspired by Vitali et al. (2006). Despite a poorer memory recall overall for aMCI patients, both groups showed enhanced recall of isolated words when they appear in 120-point or 150-point font, but not in 90-point font. Compared to the other words that were all in 60-point font, the 90-point isolated probably did not stand out sufficiently. A sufficient degree of salience or distinctiveness seems thus needed to boost memory. This fits with the classical interpretation of the Von Restorff effect, namely the distinctiveness hypothesis suggesting that different items appearing in the context of a series of similar items are better remembered (Hunt, 1995). Of note, it is suggested that this is not the difference in itself which promotes memory, but rather the fact that it occurs against the lack of discriminability and memorability of other items that are similar to each other (Hunt, 1995; Tulving & Rosenbaum, 2006; Von Restorff, 1933). Our results support the preservation of the boosting effect of isolation-related novelty on subsequent recall in aMCI patients, supported by the Bayesian analysis suggesting moderate evidence for the absence of group differences.

However, compared to control participants, our results showed that the primacy effect, which is sometimes described as related to contextual novelty (Davelaar, 2013), was diminished in aMCI patients. This finding supports previous research from Cunha et al. (2012) or Howieson et al. (2011). Nevertheless, there exist alternative explanations to the primacy effect. A usual interpretation is that there is more opportunity for rehearsal and consolidation of the first items and that proactive interference is reduced as there are no or few previous items. In that context, the involvement of novelty-related processes in the primacy effect is unclear.

Overall, our results highlight a potential preservation of contextual novelty detection as well as novelty boosting effects on memory in a population of aMCI patients. This deviates from the observations reported by previous studies in groups of patients with a diagnosis of probable Alzheimer's disease (Daffner et al., 2001; Vitali et al., 2006). On the one hand, as already mentioned, Daffner et al. (2001) reported an absence of novelty preference in demented patients. On the other hand, Vitali et al. (2006) demonstrated that the boosting effect of novelty on memory is reduced in patients compared to healthy controls. These discrepancies with our results could reflect the preservation of novelty-related processes in the initial stages of evolutive memory impairment such as Alzheimer's disease. Indeed, unlike previous studies, we included only patients with a memory decline who did not meet dementia criteria—that is an earlier stage. The next step would be to directly compare groups of patients at different stages on the same versions of the tasks. Moreover, aMCI is a heterogeneous condition and not all aMCI patients do progress to dementia of the Alzheimer type in subsequent years (Peterson & Negash, 2008). It may be that only those aMCI patients who are in the prodromal phase of Alzheimer's disease demonstrate impaired processing of novelty. This could be evaluated in longitudinal studies comparing novelty-related performance as a function of whether aMCI patients progressed or not to dementia in the subsequent years.

For the first time, our results suggest a potential preservation of novelty-related memory enhancement in patients with mild memory impairment. This result is far from trivial since this could lead to direct clinical applications. New rehabilitation strategies could possibly rely on these processes to enhance memorization and decrease the impact of the memory impairment in daily activities and social relationships. For example, if it is important to a family member that the patient remembers a specific event (e.g., a birthday visit), the relative could be taught how to make this event distinctive and novel to increase the likelihood of later memory. Future studies could focus on the relevance and robustness of novelty boosting effect in ecological context and daily situations. As a transitional step towards this goal, one can imagine using virtual reality paradigms to study novelty effects in more ecological, but sufficiently controlled environments (see examples, Schomaker et al., 2014; Schomaker & Wittmann, 2021).

Also, it is important to keep in mind that even though memory performance of aMCI patients was boosted by novelty (i.e., they recalled isolated words significantly better than other words), they recalled less isolated words than the healthy control participants did. By consequence, although novelty can enhance memorization, it is not sufficient to normalize the performance of patients. Moreover, in control participants, we observed a negative relationship between memory performance and boosting memory effect of novelty, which, despite its lack of statistical significance, suggests that people with better memory exhibit smaller gain factors. This seems true only until a certain level of memory impairment since that correlation was not observed in aMCI patients who have worse memory performance. It is possible that the relation between memory and novelty is not linear.

Besides clinical applications, the preservation of the boosting effect of isolation-related novelty on subsequent recall despite impaired episodic memory in the aMCI patients is interesting to consider in the light of divergent theoretical viewpoints relative to the relationship between novelty and memory, as either parts of the same continuum (Brown et al., 2002; Kumaran & Maguire, 2007) or independent functions (Kafkas & Montaldi, 2014). Our results rather support the second theory, and are compatible with the recent framework proposed by Kafkas and Montaldi (2018). The latter suggests that there would be different novelty detection systems (depending on the nature of novelty: absolute or contextual) which would interact differently with the episodic memory system. Absolute novelty would be processed as an absence of familiarity by the perirhinal cortex, which assesses the degree of novelty/familiarity on a continuum. Otherwise, contextual novelty would be detected by the hippocampus (Kafkas & Montaldi, 2018), which is thought to be coupled with two distinct brain networks in order to generate two mutually exclusive brain states: one for novelty processing and the other for remembering (Barbeau et al., 2017). In our study, the absence of significant correlation in aMCI patients between the free recall memory performance on the Free and Cued Selective Reminding Test on the one hand, and the gain factor on the von Restorff paradigm or the intensity of novelty preference on the oddball paradigm, on the other hand, could also be interpreted in that sense. However, we believe that memory and novelty may have more complex interactions, as suggested by the nonlinearity of their relationship. The preference for contextual novelty on the oddball paradigm tended to be positively correlated to memory performance in the aMCI group, but this correlation was not present in the control group. This suggests that memory and contextual novelty processes might get affected once brain regions are sufficiently altered. To assess this hypothesis, neuroimaging data for aMCI patients would provide a mean to investigate the relation between the hippocampal volume and the benefit of contextual novelty on memory given that contextual novelty is underpinned by a hippocampal dopaminergic loop (Frank & Kafkas, 2021).

Beyond this debate, also comes a new point of view considering novelty as gradual rather than all-or-nothing (Reichardt et al., 2022). For illustration purpose, what Võ (2021) describes as semantic violations – i.e., when an object is incongruent in the scene (e.g., a hairdryer in the kitchen) – and syntactic violations – i.e., when an object is semantically consistent with the overall scene, but has an unexpected structure (e.g., toothbrush in the bathtub) – could be two distinct levels of contextual novelty. This gradual aspect of novelty has not been taken into account in our study, which could constitute a limit to be overcome in future studies. As a perspective, it would be informative to also investigate other kinds of contextual novelty, such as context surprise when a familiar object is unexpectedly encountered in another context, or context novelty where the context is so new that the individual cannot predict what to expect (as described by Quent et al. (2021) for example).

Conclusion

For the first time, our study showed that preference for contextual novelty (on Oddball paradigm) and the boosting effect of isolation-related novelty on subsequent recall (on Von Restorff paradigm) seem preserved despite impaired episodic memory in aMCI patients. In the light of contemporary divergent theories regarding the relationship between novelty and memory, as either being independent or parts of a continuum, we argue that different types of novelty may have different relationships with memory: contextual novelty being potentially independent.

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Declaration of interest statement

The authors report there are no competing interests to declare.

Data availability statement

Preprocessed anonymized data are available at https://osf.io/8dnpc/?view_only=205c289ee3d343b2856d2201676c9633.

Ethical approval

Written informed consent was obtained according to the Declaration of Helsinki, and procedures were approved by the Ethics Committee (#2012/274).

Author contributions

All the authors engaged in conceptual and methodological discussions. CB and EB designed the study. AS collected and analyzed the data. AS and CB wrote the draft manuscript. EB and CB provided critical feedback and revisions. All the authors approved the final version of the manuscript before submission.

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Appendices 1. Control group: Demographic data, MMSE scores, and performance to the Free and Cued Selective Reminding Test along with comparison with the norms.

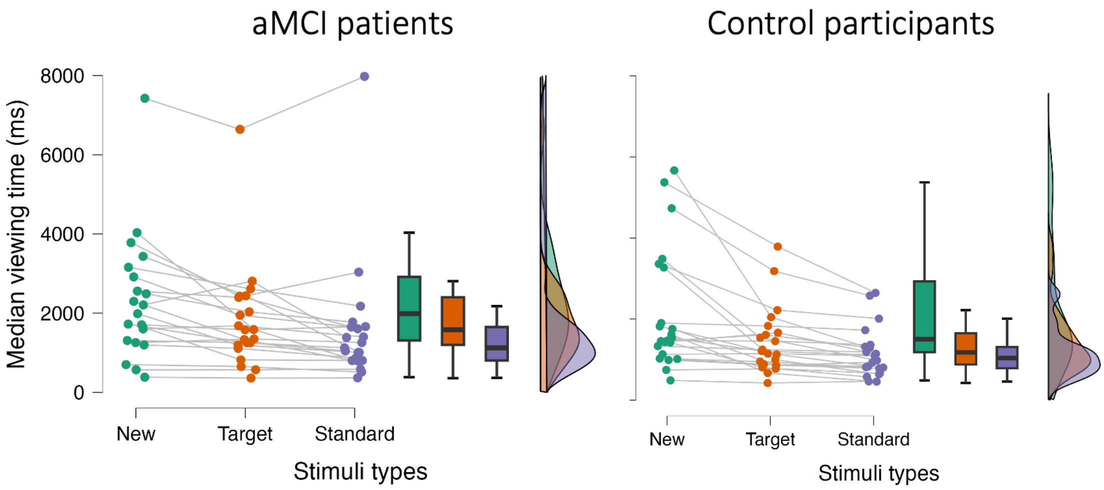
			Free and Cued Selective Reminding Test									
ID code	Sex/Age/ Education	MMSE score /30	Immediate recall /16 (z score)	Free recall 1 /16 (z score)	Total recall 1 /16 (centile)	Free recall 2 /16 (z score)	Total recall 2 /16 (centile)	Free recall 3 /16 (z score)	Total recall 3 /16 (centile)	Delayed free recall /16 (z score)	Delayed total recall /16 (centile)	Recognition hits /16 (number of false alarms)
Control 1	F/76/13	28	16 (>C50)	6 (-.95)	16 (>C75)	8 (-.74)	16 (>C50)	8 (-1.3)	16 (>C25)	10 (-.48)	16 (>C25)	16
Control 2	M/72/10	26	16 (>C50)	8 (.02)	14 (C25)	7 (-.98)	14 (C5-25)	9 (-.73)	16 (>C25)	11 (.13)	16 (>C25)	16
Control 3	M/61/12	30	15 (C25)	6 (-1.36)	13 (C5-25)	9 (-.68)	14 (C5-25)	9 (-1.35)	16 (>C25)	11 (-.52)	16 (>C25)	16
Control 4	F/82/8	29	16 (>C50)	7 (-.31)	16 (>C75)	9 (.02)	14 (C5-25)	8 (-.96)	15 (C5-25)	8 (-1.07)	16 (>C25)	16
Control 5	M/71/20	28	16 (>C50)	9 (.29)	16 (>C75)	10 (.02)	14 (C5-25)	9 (-1.08)	16 (>C25)	10 (-.64)	16 (>C25)	16
Control 6	M/59/12	29	15 (C25)	10 (.48)	16 (>C75)	9 (-.68)	15 (C25)	10 (-.90)	16 (>C25)	13 (.39)	16 (>C25)	16
Control 7	M/71/14	30	16 (>C50)	8 (-.17)	12 (C5)	10 (.02)	13 (C5)	12 (.27)	14 (C5)	11 (-.19)	15 (C5-25)	16
Control 8	F/71/11	28	16 (>C50)	6 (-1.14)	14 (C25)	11 (.48)	15 (C25)	13 (.84)	16 (>C25)	14 (1.17)	16 (>C25)	16
Control 9	M/65/15	29	16 (>C50)	11(1.21)	16 (>C75)	9 (-.42)	15 (C25)	10 (-.63)	15 (C5-25)	13 (.72)	16 (>C25)	15 (1)
Control 10	M/71/10	29	16 (>C50)	8 (.02)	15 (C50)	12 (1.22)	16 (>C50)	12 (.62)	16 (>C25)	13 (1.04)	16 (>C25)	16
Control 11	F/73/15	30	16 (>C50)	11 (.97)	15 (C50)	9 (-.72)	16 (>C50)	12 (.04)	16 (>C25)	13 (.40)	16 (>C25)	16
Control 12	F/65/13	29	16 (>C50)	9 (.06)	14 (C25)	10 (-.28)	16 (>C50)	14 (.94)	16 (>C25)	13 (.40)	16 (>C25)	16
Control 13	F/66/11	28	16 (>C50)	11 (1.16)	16 (>C75)	10 (.04)	16 (>C50)	12 (.39)	16 (>C25)	12 (.26)	16 (>C25)	16
Control 14	F/68/13	30	16 (>C50)	10 (.51)	15 (C50)	11 (.16)	15 (C25)	13 (.49)	16 (>C25)	11 (-.51)	16 (>C25)	16
Control 15	F/72/13	30	16 (>C50)	9 (.06)	16 (>C75)	12 (.60)	16 (>C50)	14 (.94)	16 (>C25)	14 (.85)	16 (>C25)	16
Control 16	F/63/10	28	16 (>C50)	11 (.79)	16 (>C75)	12 (.51)	16 (>C50)	14 (.85)	16 (>C25)	15 (1.13)	16 (>C25)	16
Control 17	M/75/17	28	16 (>C50)	12 (2.04)	16 (>C75)	13 (1.76)	16 (>C50)	13 (1.16)	16 (>C25)	12 (.76)	16 (>C25)	16
Control 18	F/69/12	28	16 (>C50)	10 (.61)	16 (>C75)	14 (1.64)	16 (>C50)	14 (1.12)	16 (>C25)	14 (1.01)	16 (>C25)	16
Control 19	F/82/6	29	15 (C25)	11 (1.52)	16 (>C75)	14 (2.22)	16 (>C50)	14 (1.74)	16 (>C25)	13 (1.20)	16 (>C25)	16
Control 20	F/65/8	29	16 (>C50)	12 (1.61)	16 (>C75)	13 (1.37)	16 (>C50)	15 (1.74)	16 (>C25)	16 (2.08)	16 (>C25)	16
Control 21	F/67/15	30	16 (>C50)	13 (1.89)	16 (>C75)	14 (1.48)	16 (>C50)	15 (1.39)	16 (>C25)	15 (1.30)	16 (>C25)	16
Control 22	F/52/12	30	16 (>C50)	14 (2.07)	16 (>C75)	15 (1.67)	16 (>C50)	15 (1.12)	16 (>C25)	16 (1.43)	16 (>C25)	16

Appendices 2. aMCI group: Demographic data, MMSE scores, and performance to the Free and Cued Selective Reminding Test along with comparison with the norms.

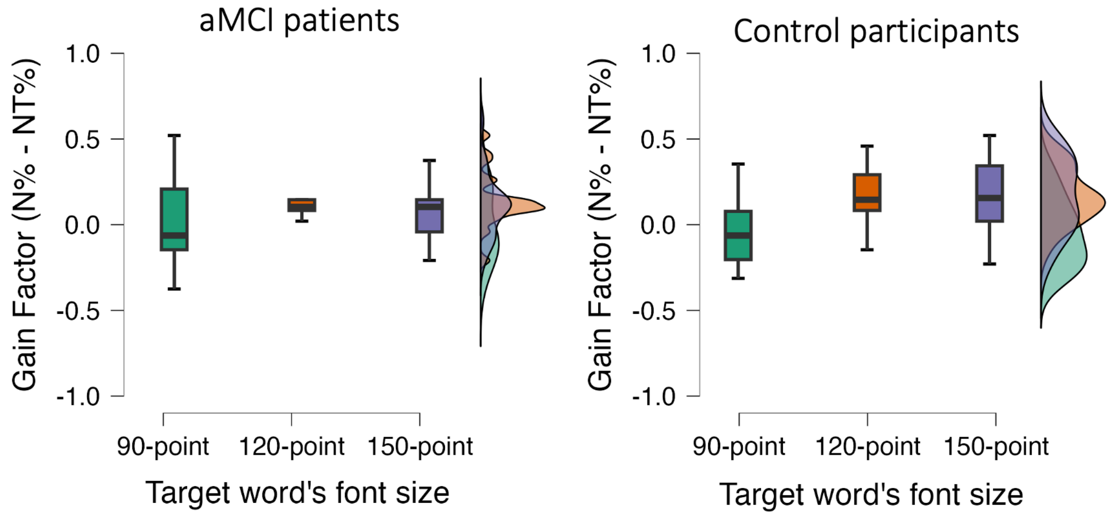
ID code	Sex/Age/ Education	MMSE score /30	Free and Cued Selective Reminding Test									
			Immediate recall /16 (z score)	Free recall 1 /16 (z score)	Total recall 1 /16 (centile)	Free recall 2 /16 (z score)	Total recall 2 16 (centile)	Free recall 3 /16 (z score)	Total recall 3 16 (centile)	Delayed free recall /16 (z score)	Delayed total recall 16 (centile)	Recognition hits /16 (number of false alarms)
aMCI 1	M/69/12	23	16 (>C50)	2 (-2.83)*	12 (C1-5)*	1 (-3.78)*	11 (C1-5)*	2 (-4.04)*	10 (<C1)*	0 (-5.03)*	7 (<C1)*	15 (9)
aMCI 2	F/58/17	23	14 (C5-25)	3 (-3.06)*	8 (C1)*	3 (-3.78)*	10 (C1-5)*	1 (-5.33)*	7 (<C1)*	0 (-6)*	6 (<C1)*	13 (9)
aMCI 3	F/72/15	23	13 (C5)	5 (-1.78)*	12 (C5)	3 (-3.37)*	12 (C1-5)*	2 (-4.44)*	12 (C1)*	3 (-4.15)*	12 (C1-5)*	/
aMCI 4	M/71/18	29	14 (C5-25)	4 (-2)*	14 (C25)	5 (-2.19)*	15 (C25)	7 (-1.97)*	14 (C5)	5 (-2.91)*	14 (C5)	16
aMCI 5	F/79/12	23	9 (<C1)*	5 (-1.23)	6 (<C1)*	4 (-2.18)*	12 (C1-5)*	7 (-1.40)	13 (C1-5)*	0 (-4.70)*	10 (<C1)*	/
aMCI 6	M/81/16	25	12 (C1-5)*	6 (-.72)	9 (C1-5)*	5 (-1.77)*	11 (C1-5)*	6 (-1.98)*	14 (C5)	2 (-3.79)*	8 (<C1)*	/
aMCI 7	M/65/10	29	16 (>C50)	4 (-1.82)*	13 (C5-25)	7 (-.98)	15 (C25)	7 (-1.62)	14 (C5)	7 (-1.69)*	14 (C5)	13
aMCI 8	M/76/15	30	15 (C25)	3 (-2.09)*	14 (C25)	7 (-.89)	16 (>C50)	9 (-.63)	14 (C5)	10 (-.15)	16 (>C25)	/
aMCI 9	M/59/9	26	13 (C5)	5 (-1.72)*	10 (C1-5)*	8 (-.96)	10 (C1-5)*	7 (-2.07)*	11 (<C1)*	10 (-.81)	13 (C1-5)*	/
aMCI 10	M/65/15	27	15 (C25)	6 (-1.08)	14 (C25)	7 (-1.3)	14 (C5-25)	7 (-1.97)*	16 (>C25)	6 (-2.46)*	16 (>C25)	15
aMCI 11	F/64/8	27	15 (C25)	7 (-1.05)	13 (C5-25)	8 (-1.26)	14 (C5-25)	5 (-3.19)*	15 (C5-25)	10 (-1.14)	16 (>C25)	15
aMCI 12	M/66/12	28	16 (>C50)	6 (-.99)	15 (C50)	6 (-1.58)	15 (C25)	9 (-.90)	14 (C5)	7 (-1.85)*	13 (C1-5)*	14
aMCI 13	M/70/21	28	14 (C5-25)	3 (-2.46)*	16 (>C75)	9 (-.42)	16 (>C50)	9 (-1.08)	15 (C5-25)	9 (-1.10)	16 (>C25)	/
aMCI 14	F/70/12	29	15 (C25)	6 (-1.32)	13 (C5-25)	6 (-1.88)*	15 (C25)	9 (-1.30)	15 (C5-25)	10 (-.97)	16 (>C25)	/
aMCI 15	M/68/15	29	16 (>C50)	7 (-.62)	13 (C5-25)	8 (-.86)	14 (C5-25)	7 (-1.97)*	15 (C5-25)	8 (-1.55)	14 (C5)	/
aMCI 16	M/69/17	28	16 (>C50)	8 (-.17)	11 (C1-5)*	9 (-.42)	14 (C5-25)	8 (-1.52)	16 (>C25)	12 (.27)	15 (C5-25)	16
aMCI 17	F/77/13	28	16 (>C50)	6 (-.95)	11 (C1-5)*	10 (.14)	16 (>C50)	11 (.04)	16 (>C25)	13 (.89)	16 (>C25)	16
aMCI 18	M/80/13	28	16 (>C50)	8 (.20)	16 (>C75)	13 (1.76)	16 (>C50)	6 (-1.98)*	13 (C1-5)*	12 (.76)	14 (C5)	16
aMCI 19	F/77/8	25	12 (C1-5)*	8 (.15)	13 (C5-25)	12 (1.34)	16 (>C50)	11 (.39)	16 (>C25)	13 (1.20)	16 (>C25)	/
aMCI 20	F/57/16	28	16 (>C50)	10 (.15)	16 (>C75)	12 (.18)	16 (>C50)	9 (-1.74)*	16 (>C25)	13 (-.10)	16 (>C25)	16
aMCI 21	F/75/14	28	16 (>C50)	11 (1.34)	15 (C50)	13 (1.46)	16 (>C50)	10 (-.41)	15 (C5-25)	7 (-1.84)*	14 (C5)	16

Note. The scores in red* indicate a performance lower than the norms and "/" indicates a missing value

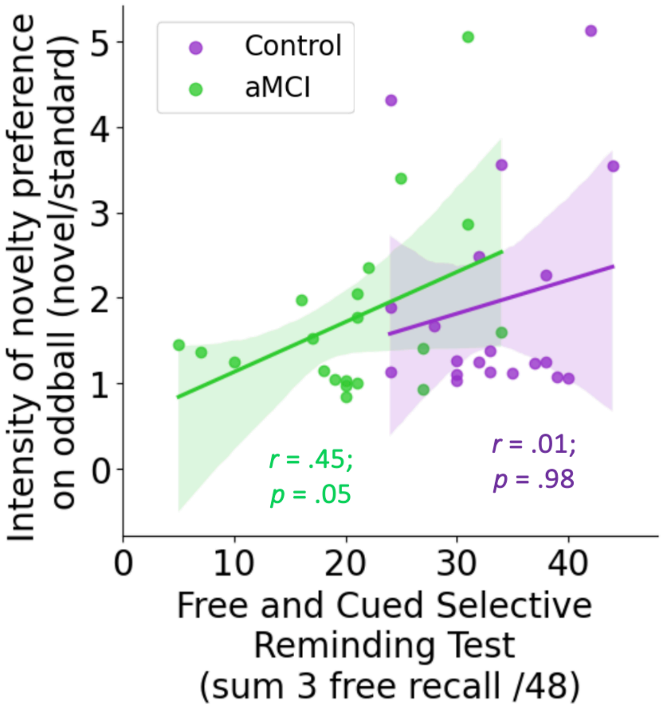
Appendices 3. Individual median viewing times (VTs) for aMCI patients (on the left) and control participants (on the right) on the oddball paradigm.



Appendices 4. Boxplots of the gain factor (GF) on the Von Restorff paradigm depending on the target word's font size for each group.



Appendices 5. Scatter plots of the correlations between the intensity of novelty preference on the oddball paradigm (median VTs for novel stimuli/median VTs for standard stimuli) and the performance on the free recalls from the Free and Cued Selective Reminding test for each group.



Appendices 6. Scatter plots of the correlations between the gain factor (GF%) on the Von Restorff paradigm and the performance on the free recalls from the Free and Cued Selective Reminding test (/48) for each group. r: value of the Pearson's correlation, p: p-value of the correlation test.