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The antimuscarinic agent biperiden selectively impairs recognition of abstract figures without affecting the processing of non-words

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Abstract

Objectives: The present study investigated the effects of biperiden, a muscarinic type 1 antagonist, on the recognition performance of pre-experimentally unfamiliar abstract figures and non-words in healthy young volunteers. The aim was to examine whether 4 mg biperiden could model the recognition memory impairment seen in healthy aging.

Methods: A double-blind, placebo-controlled, two-way crossover study was conducted. We used a three-phase (deep memorization, shallow memorization, and recognition) old/new discrimination paradigm in which memory strength was manipulated. Strong memories were induced by deep encoding and repetition. Deep encoding was encouraged by redrawing the abstract figures and mentioning existing rhyme words for the non-words (semantic processing). Weak memories were created by merely instructing the participants to study the stimuli (shallow memorization).

Results: Biperiden impaired recognition accuracy and prolonged reaction times of the drawn and the studied abstract figures. However, participants were biased towards "old" responses in the placebo condition. The recognition of the new abstract figures was unaffected by the drug. Biperiden did not affect the recognition of the non-words.

Conclusions: Although biperiden may model age-related deficits in episodic memory, the current findings indicate that biperiden does not mimic age-related deficits in recognition performance.

KEYWORDS
abstract pictures, biperiden, cognitive aging models, healthy aging, non-words, recognition memory

1 | INTRODUCTION

It is well-established that healthy aging is associated with memory impairments. However, the effect of aging on memory seems to depend on which memory functions are being investigated. For example, aging seems to impair episodic memory most consistently, whereas semantic memory, working memory, and procedural memory remain to a great extent intact in healthy elderly (Nilsson, 2003). Furthermore, age-related impairments are typically found in recognition memory tests (Fraundorf et al., 2019; Rhodes et al., 2019). In recognition memory paradigms, participants must recognize previously studied stimuli as "old" correctly and identify not presented ones as "new" (Malmberg, 2008).

However, the aging effect on recognition memory seems to depend on the stimulus's nature (i.e., identifying a stimulus as "old" or "new"). Age appears to decrease stimulus discriminability (Fraundorf et al., 2019; Wolk et al., 2009), which is typically related to a tendency to judge presented stimuli as "old" despite them being new (Gallo et al., 2007; Kroll et al., 1996). It seems likely that these performance differences are at least partly due to an impairment in sensitivity to novelty (Czigler et al., 2006; Daffner et al., 2006, 2011). Another factor could be the limited availability of processing resources in older age (Park & Festini, 2017). A final factor could be the age-related slowing in processing speed (Levin et al., 1992; van Hooren et al., 2007). Salthouse (1996) proposed that this reduction in processing speed contributes to delayed cognitive process execution and the loss of information processed at earlier stages.

In addition to novelty processing, the level of processing (LOP) also seems to affect recognition performance in aged people (Fraundorf et al., 2019). The LOP theory predicts that deep (e.g., via mnemonics, meaning-extraction, pattern recognition, and activation of prior knowledge) and intermediate processing (e.g., phonetics) lead to superior and faster retrieval when compared to shallow processing (e.g., perceptual analyses, rehearsal) (Craik, 2002; Craik & Lockhart, 1972; Craik & Tulving, 1975; Newell & Andrews, 2004). Fraundorf et al. (2019) reported that age differences were larger when deep semantic encoding was applied compared to shallow processing. This may be related to age-related difficulties with self-initiation of deep encoding strategies. Thus, when such strategies are provided age differences were not found (Craik & Rose, 2012; Froger et al., 2009; Logan et al., 2002).

In previous studies, it has been shown that selective blocking of muscarinic type 1 (M1) receptors specifically impairs episodic memory (Borghans et al., 2017, 2020; Sambeth et al., 2015; Vingerhoets et al., 2017; Wezenberg et al., 2005). In these studies, it was found that the M1 antagonist biperiden (BIP) impaired the performance in the verbal learning task (VLT) but did not affect working memory, as measured by the n-back task. These effects appeared to be selective memory impairments since BIP treatment did not affect the performance in attention tasks. These results suggest that BIP treatment could be a suitable pharmacological model of age-related episodic memory impairment.

Characterizing BIP's effects can aid a better understanding of which neurotransmitter systems may underlie the age-related memory deficits. This is relevant from a scientific viewpoint, and it may be relevant for the development of treatments for age-related memory deficit. This could be an M1 agonist such as BIP. To further investigate the validity of BIP as a pharmacological model of age-related memory impairment, we examined the effect of BIP on old/new discrimination performance using pre-experimentally unfamiliar stimuli in a sample of healthy young participants. We applied a three-phase old/new discrimination memory paradigm with abstract figures and non-words (Toth et al., 2021). Memory strength was manipulated as a function of LOP (Craik, 2002; Craik & Lockhart, 1972; Craik & Tulving, 1975; Newell & Andrews, 2004) and repetition (Hintzman & Curran, 1997; Ranganath & Rainer, 2003). Repetition is known to strengthen memory by increasing the subjective sense of familiarity resulting from the re-encoding of a particular memory trace (Hintzman & Curran, 1997; Ranganath & Rainer, 2003). In the current experiment, we first familiarized the stimuli using mnemonics to induce deep processing (deep memorization): the participants were asked to redraw the abstract figures and to mention existing rhyming words for the non-words (semantic processing). In the second phase, participants were asked to merely study the stimuli (shallow memorization). Here, the previously deeply encoded items were shown again in combination with some new items. Finally, an old/new recognition test was applied in which stimuli from the first and second phases were intermixed with new ones. Both recognition accuracy and speed were assessed.

Based on previous studies in healthy aging, we did not anticipate detecting drug effects on the overall correct old item recognition (drawn/semantically encoded and studied items). However, we anticipated lower discriminability indexes due to higher false alarm rates (incorrectly identifying new items as "old"), and slower reaction times as a consequence of drug treatment. Furthermore, we anticipated that BIP would decrease the number of correctly rejected new items. Also, we expected that BIP would increase the false alarm rates in response to the new stimuli presented only during the recognition phase. Finally, we hypothesized that in the BIP as well as the placebo (PLA) sessions, deep memorization and repetition would prompt better recognition than shallow memorization without repetition. In other words, items relying on strong memory would be better recognized than those relying on weak memory.

2 | METHODS

2.1 | Participants

Based on previous studies using the current paradigm, an *a priori* statistical power analysis using G*power 3.1 showed that in order to detect significant behavioral effects using an ANOVA, 19 participants were required with an effect size of 0.4 and power of at least 90% at a significance level of 5% (Faul et al., 2007). Therefore, 21 healthy volunteers between the age of 18 and 35 years were recruited. One

participant terminated the study due to personal reasons, and thus, was excluded from further analyses. The final dataset contains 20 participants (five males, with a mean age of 23 years) who were students from Maastricht University, with the highest education level being pre-university education or bachelor's degree. Inclusion was based on medical screening, which involved filling in a medical questionnaire followed by a detailed examination by a physician. Blood and urine tests were taken to confirm the participants' health condition and to rule out the apparent use of psychoactive drugs (e.g., cannabinoids, methylphenidate, cocaine, amphetamine, antidepressants, etc.), pregnancy or lactation. Furthermore, participants were included if their body mass index fell within the range of 18.5–30 kg/m^2.

Participants were excluded in case of hypersensitivity to any component of the formulation of BIP or related compounds. Further exclusion criteria comprised smoking, excessive drinking (>20 glasses of alcohol-containing beverages a weak), use of medication other than oral contraceptives, and any sensory or motor deficits, which could have affected test performance. Participants with neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine diseases were also ruled out. Additionally, participants were excluded if they had a history of psychiatric conditions, such as ADHD, schizophrenia, different forms of depression, anxiety, mood and personality disorders, or addiction.

This study was conducted according to the codes of ethics on human experimentation established by the declaration of Helsinki (1964) and amended in Fortaleza (2013), and in accordance with the Medical Research Involving Human Subjects Act (WMO; World Medical Association, 2013). The Medical Ethics Committee approved the study of the University Hospital Maastricht and Maastricht University. Medical Ethical Approval Code: EPU-P95A NL58970.068.16. Each participant received monetary compensation or research participation credit points.

2.2 | Study design and medication

A randomized, double-blind placebo (PLA) controlled two-way crossover design was applied with a counterbalancing of orders over the two sessions. This means that each participant was tested two times on two separate occasions, once receiving 4 mg BIP (Akineton®) and once PLA. The order of treatment (PLA-BIP and BIP-PLA) was balanced in the sample. The washout period was 7–14 days. The order of the medications was blinded. Treatment was applied in accordance with previous results showing that peak plasma levels of BIP are reached 60–90 min after intake of a single dose (Sudo et al., 1998).

2.3 | Procedure

Volunteers provided informed consent before the medical examination. Hereafter, they received training to be familiarized with the test procedures. A test battery was used during this training session, which contained a different set of stimuli from those used during the actual test days. This was done to avoid learning effects. Hereafter, the test days were scheduled within a maximum of seven days after the training session. The two testing days were scheduled at the exact same time of the day to reduce diurnal effects.

Before and after the testing sessions, participants filled in questionnaires assessing their general well-being status and possible complaints (e.g., headache, drowsiness, sweating, and sleepiness). Participants had to indicate whether they experienced any of the 33 possible complaints on a four-point scale. For example, a score of zero stood for "I do not experience this complaint at all," and a three stood for "I am experiencing this complaint strongly." If the participants experienced any complaints not listed on the questionnaire, they were asked to mention them on the questionnaire form in writing. Scores were compared between the different time points to examine treatment-induced side effects. Adverse events were monitored using printed forms.

Subsequently, 90 min before the behavioral testing, medication (BIP or PLA) was administered. The participants were asked to refrain from alcohol, smoking, and caffeine 12 h before testing and not to use drugs throughout the study.

A memory paradigm with abstract figures and non-words was applied in separate tests (Toth et al., 2021). See Figure 1 for an example of the stimuli used. Every participant performed each test phase first with the abstract figures and then with the non-words to minimize the verbalization of the figurative stimuli. The experiment consisted of three phases (see Figure 2). In phase 1 (deep memorization leading to "strong" memory), participants were familiarized with a series of 15 monosyllabic abstract figures or non-words in separate tests (list 1: L1). Participants were asked to manually redraw the abstract figures on an answer sheet to induce deep LOP. They had to mention existing English or Dutch rhyming words for each non-word to induce intermediate LOP. Stimuli were presented for 1 s, and the participants were given 14 s to execute the mnemonic encoding task. If they were ready earlier, they could press a button, and 2 s later, the next stimulus appeared. Stimuli were extracted from previous studies (Glosser et al., 1998; Redoblado et al., 2003; Seidenberg et al., 1994).

During phase 2 (shallow memorization leading to "weak" memory), participants were instructed to remember as many stimuli as possible. In this phase, 30 stimuli (abstract figures or non-words) were used: 15 stimuli from L1 were randomly mixed with 15 new ones (L2). All stimuli were shown for 1 s with an inter stimulus interval (ISI) of 2 s.

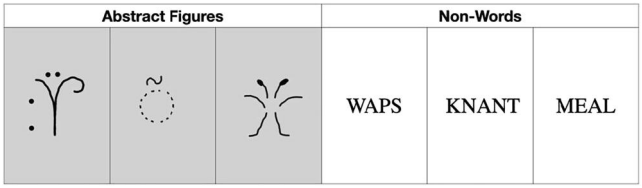

FIGURE 1 Examples of the stimuli used

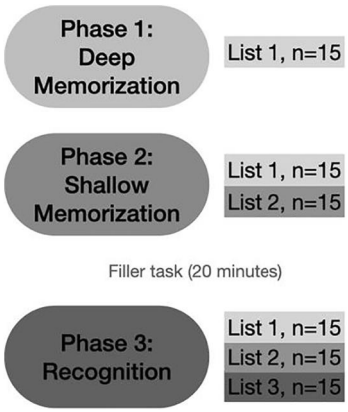

FIGURE 2 Schematic overview of the experimental design. Phase 1: deep memorization with the pre-experimentally unfamiliar abstract figures and non-words in separate tests using a mnemonic encoding task (redrawing the abstract figures and mentioning rhyming words for the non-words). The 15 stimuli used here form List 1 (drawn/semantically processed stimuli). Phase 2: shallow memorization with the instruction to remember as many stimuli as possible. This phase contained items from List 1 and 15 new ones (List 2, studied stimuli). Phase 3: recognition of the stimuli including List 1, List 2, and 15 new (List 3). *n*: number of stimuli presented

During phase 3, participants were asked to decide if they had seen the presented stimulus in the previous series (L1 and L2) or whether the stimulus was new to them (L3: new, $n = 15$). The 45 non-words or abstract figures were presented for a duration of 1 s, or less in case of faster button press; the ISI was 2.5 s. Participants had to press the corresponding buttons ("old" for L1 and L2, or "new" for L3 stimuli) on a response box as quickly and accurately as possible.

The Attention Network Test was administered between phase 2 and 3 as a filler task lasting 20 min (Togo et al., 2015).

2.4 | Data analysis

Before analysis, all data were evaluated for having normal distribution and homogeneity of variance. Also, raw data were checked for outliers. Outlier values were replaced with their regression estimates produced by the Missing Value Analyses (IBM SPSS Statistics for Macintosh, Version 27.0. Armonk, NY: IBM Corporation). Additionally, due to technical issues, 1–2 responses per participant were missing (e.g., the button press was not recorded). In these cases, values were replaced with their regression estimates. Effect sizes are reported based on partial eta-squared (ηp^2) data. Furthermore, Mauchly's Test of Sphericity was applied. In case the assumption of sphericity was violated, a Greenhouse-Geisser correction was used. In all cases, degrees of freedom of assumed sphericity are reported. Post hoc comparisons and simple effects were investigated using paired samples *t*-tests, applying adjustments for multiple comparisons; the observed *p*-values were multiplied by the number of comparisons, which was tested against the set significance level of .05.

For the behavioral data, Signal Detection Theory (SDT) was applied in order to investigate the discrimination performance (Benjamin & Bawa, 2004; Benjamin et al., 2009; Stanislaw & Todorow, 1999; Verde & Rotello, 2007). Discrimination accuracy was defined as the ability to distinguish the different types of stimuli (drawn/semantically processed, studied, and new). Correct responses included an "old" response to the drawn/semantically processed items, and the studied stimuli, and a "new" response to the new items. Incorrect responses involved a "new" response to the drawn/semantically processed items and the studied stimuli and an "old" response to the new stimuli. See Table 1 for an overview.

Given the memory strength manipulation in the current design (deep memorization, shallow memorization and recognition), the correct response rates, being hit rates (HR) for the drawn/semantically processed and the studied items and correct rejection rates (CRR) for the new, were used to evaluate the discrimination accuracy. Furthermore, in order to investigate discriminability, non-parametric A′ statistics were computed for the drawn/semantically processed and the studied stimuli using Equations (1 or 2) (Snodgrass & Corwin, 1988; Stanislaw & Todorow, 1999). A′ varies from 0 to 1 with 0.5 indicating chance performance. Higher values are indicative of improved performance (Snodgrass & Corwin, 1988; Stanislaw & Todorow, 1999).

$$A' = 0.5 + \frac{([\mathrm{HR} - \mathrm{FAR}] \times [1 + \mathrm{HR} - \mathrm{FAR}])}{(4\mathrm{HR}[1 - \mathrm{FAR}])}, \quad \text{if } \mathrm{HR} \geq \mathrm{FAR} \qquad (1)$$

$$A' = 0.5 - \frac{([\mathrm{HR} - \mathrm{FAR}] \times [1 + \mathrm{HR} - \mathrm{FAR}])}{(4\mathrm{HR}[1 - \mathrm{FAR}])}, \quad \text{if } \mathrm{HR} < \mathrm{FAR} \qquad (2)$$

A': discriminability index, HR: hit rate, FAR: false alarm rate

During recognition, the *a priori* probabilities of old and new items and the quality of the match between a test item and the memory for studied items can influence the bias parameter (Huang & Ferreira, 2020; Stanislaw & Todorow, 1999). Such a model does not fit the current paradigm due to the memory strength manipulation used and the equivalent proportion and intended comparison of the drawn/semantically processed ($n = 15$), studied ($n = 15$), and new items ($n = 15$; Benjamin & Bawa, 2004). After all, the final proportion of "old" and "new" responses was 2:1. Therefore, we calculated the total amount of "old" (H + FA) and "new" (M + CR) responses given by the participants. This was done to examine whether there was a preference for either the "old" or "new" responses. Results were compared using paired samples *t*-tests with Bonferroni corrections.

RT data of the hits were evaluated, as well. To be able to use parametric tests, RT-s were transformed into |log(1/RT)| to obtain a normal distribution of the data (Osborne, 2002). Moreover, the median RT data are reported as central tendency parameters, together with the corresponding first and third interquartile ranges (Ratcliff, 1993).

Statistical analysis was conducted using SPSS 27.0. A repeated measures analysis of variance (ANOVA) was used to investigate recognition accuracy scores and RT-s for the different treatments and types of stimuli in the different categories as assessed in Phase 3.

Thus, the within-subject variables for the abstract figures and the non-words were treatment (BIP and PLA), and stimulus type (drawn/semantically processed, studied, and new items). Finally, treatment effects per stimulus type were evaluated using individual *t*-tests, which were corrected for multiple comparisons.

3 | RESULTS

Although there was an unequal number of old responses over new responses (2:1), we found that there was no response bias towards old responses. However, the participants made more old responses and less new responses in case of the abstract figures in the PLA sessions ($p < .001$; see Table 2). Additionally, there were hardly any missing responses in the BIP (abstract figures: 3.6%, non-words: 1.56%) and in the PLA (abstract figures: 0.4%, non-words: 1.4%) session.

3.1 | Abstract figures

3.1.1 | Accuracy data

When analyzing the accuracy scores (HR and CRR) in the session with the abstract figures the ANOVA revealed a main effect of treatment ($F[1,19] = 7.44$, $\eta p^2 = 0.28$, $p < .013$) and stimulus type ($F[2,38] = 66.02$, $\eta p^2 = 0.78$, $p < .001$; see Figure 3). Moreover, the interaction term treatment × stimulus type was also significant ($F[2,38] = 10.20$, $\eta p^2 = 0.35$, $p < .003$; see Figure 3). Simple effects analyses revealed that BIP compared to the PLA impaired correct recognition of the drawn ($t[19] = 3.26$, $p < .012$) and studied ($t[26] = 3.24$, $p < .012$) but not the new abstract figures ($t[19] = 1.91$, $p > .210$).

The analyses with respect to stimulus type showed that in the sessions with BIP, participants could more accurately identify the drawn than the studied ($t[19] = 7.70$, $p < .001$; see Table 3), and the new than the studied items ($t[19] = 6.28$, $p < .001$; see Table 3). No such difference was detected between the drawn and new abstract figures ($t[19] = 0.14$, $p > .999$; see Table 3). The same analyses in the session with PLA revealed that participants could more accurately recognize the drawn stimuli compared to the weak ($t[19] = 6.45$, $p < .001$; see Table 3) and compared to the new items ($t[19] = 3.87$, $p < .003$; see Table 3). Also, more new stimuli were correctly endorsed compared to the studied items ($t[19] = 3.35$, $p < .009$).

The analyses performed on the A′ scores of the abstract figures resulted in a significant main effect of stimulus type ($F[1,19] = 112.14$, $\eta p^2 = 0.86$, $p < .001$; see Table 3). Post hoc tests showed that the participants could discriminate the drawn items more easily than the studied ($p < .001$). Moreover, the treatment × stimulus type interaction was found to be significant ($F[1,19] = 8.93$, $\eta p^2 = 0.032$, $p < .008$; see Table 3). Simple effects analyses revealed no treatments effects ($t[19] = 1.81$, $p > .172$; $t(19) = 1.67$, $p > .218$, respectively; see Table 3). However, in both the PLA and the BIP session it was easier to discriminate the drawn than the studied items ($t[19] = 6.58$, $p < .001$; $t[19] = 9.35$, $p < .001$, respectively; see Table 3). No main effect of treatment was found ($F[1,19] = 0.02$, $\eta p^2 = 0.01$, $p > .893$).

3.1.2 | Reaction time data

The ANOVA within this category confirmed a significant main effect of treatment ($F[1,19] = 9.11$, $\eta p^2 = 0.32$, $p < .007$) and stimulus type ($F[2,18] = 68.69$, $\eta p^2 = 0.88$, $p < .001$). There was a

TABLE 1 Overview of the different types of responses as a function of stimulus type

	Stimulus type	Response
Hit (H)	Drawn or semantically processed/studied	"Old"
Miss (M)	Drawn or semantically processed/Studied	"New"
Correct rejection (CR)	New	"New"
False alarm (FA)	New	"Old"
Hit rate (HR)	Drawn or semantically processed/Studied	H/(H + M)
Correct rejection rate (CRR)	New	CR/(CR + FA)

TABLE 2 The total number of old and new responses during the recognition test. Data represent the means and the standard deviations of the total old and new responses and the corresponding % compared to the 90 items/stimulus category (abstract figures and non-words), and the *t*-statistics

	Placebo		Biperiden	
	Abstract figures	Non-words	Abstract figures	Non-words
Old responses	27.60 (3.21)	23.25 (6.13)	21.95 (5.91)	23.20 (3.55)
New responses	17.20 (3.17)	21.10 (5.91)	21.45 (4.99)	21.10 (4.12)
T-test	$t(19) = 7.32$, $p < .001$	$t(19) = 0.22$, $p < .830$	$t(19) = 2.15$, $p > .431$	$t(19) = 2.10$, $p > .224$

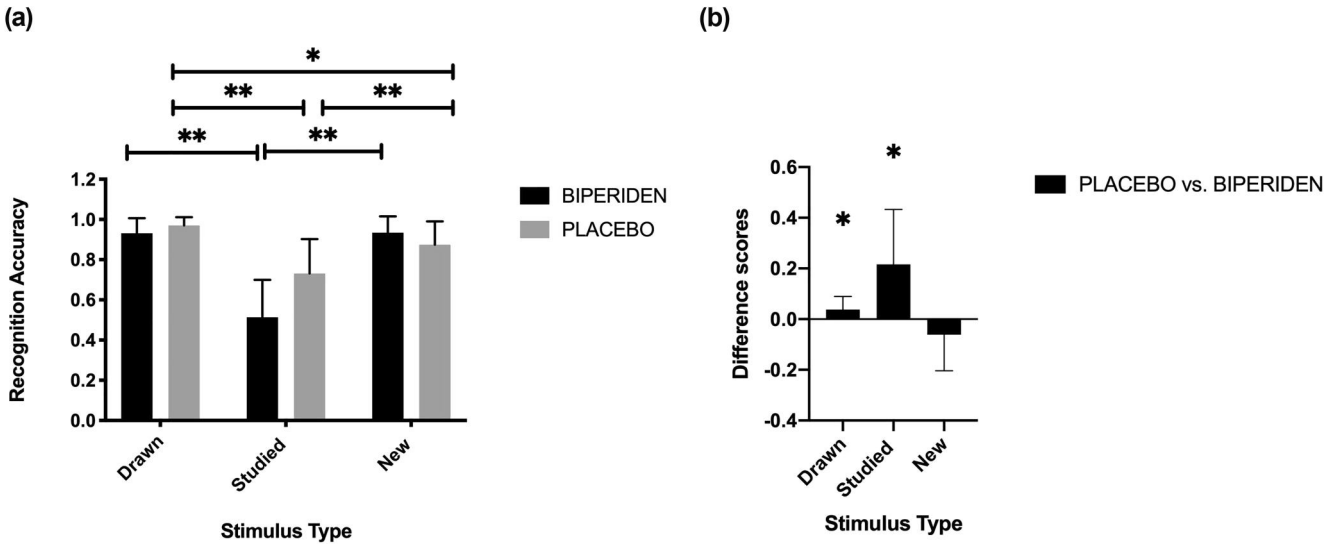

FIGURE 3 Recognition accuracy of the abstract figures according to treatment and stimulus type. The bars represent the means with the standard deviations. (a) Stimulus type effects shown as the proportion of the correct responses: hit rates for the drawn and the studied, and correct rejection rates for the new abstract figures after placebo and biperiden treatment. (b) Treatment effects depicted as the difference scores per stimulus type (drawn, studied, and new). $^{**}p < .001$, $^{*}p < .05$

TABLE 3 Means and standard deviations of the signal-detection measures during the recognition of abstract figures (drawn, studied, and new) after placebo and biperiden

Abstract figures			
Stimulus	**Parameters**	**Placebo**	**Biperiden**
Drawn	HR	0.97 (0.04)**,****	0.93 (0.08)*,**
	A′	0.82 (0.09)**	0.87 (0.19)**
Studied	HR	0.73 (0.17)	0.51 (0.19)*
	A′	0.67 (0.10)	0.62 (0.12)
New	CRR	0.87 (0.12)**	0.93 (0.08)***

Abbreviations: A', discriminability index; CRR, correct rejection rate; HR, hit rate.

Treatment effects, $^{*}p < 0.05$; Different from studied stimuli, $^{**}p < 0.001$; $^{***}p < 0.05$; Different from new stimuli, $^{****}p < 0.05$.

TABLE 4 Median reaction times (middle 50% range), and their corresponding first and third interquartile ranges in milliseconds in response to the abstract figures (drawn, studied, and new) after placebo and biperiden treatment

Abstract figures median (1-3 IQ)		
Stimulus	**Placebo**	**Biperiden**
Drawn	589 (527–628)*,****	633 (609–751)*,***,****
Weak	724 (637–793)	794 (741–886)*
New	718 (649–760)	733 (636–800)***

Treatment effects: $^{*}p < 0.05$; Different from studied stimuli: $^{**}p < 0.001$, $^{***}p < 0.05$; Different from new stimuli: $^{****}p < 0.05$.

treatment × stimulus type interaction detected ($F[2,18] = 6.36$, $\eta p^2 = 0.41$, $p > .008$; see Table 4). Simple effects analyses revealed that BIP compared to the PLA slowed the reactions in response to the drawn ($t[19] = 3.78$, $p < .003$) and the studied ($t[19] = 2.90$, $p < .027$) but not to the new abstract figures ($t(19) = 0.29$, $p > .999$). Simple effects analyses with respect to stimulus type showed that in the sessions with BIP participants reacted faster to the drawn than the studied ($t[19] = 8.23$, $p < .001$), the new than the studied items ($t[19] = 3.47$, $p < .009$) and the drawn compared to the new abstract figures ($t[19] = 3.49$, $p < .009$). Similarly, the same analyses in the session with PLA revealed that participants reacted faster to the drawn than the studied ($t[19] = 8.99$, $p < .001$) and new abstract figures ($t[19] = 7.49$, $p < .001$). No such difference was found between the studied and new items ($t[19] = 0.60$, $p > .999$).

3.2 | Non-words

3.2.1 | Accuracy data

The ANOVA analysis for the non-words revealed a main effect of stimulus type ($F[2,18] = 32.51$, $\eta p^2 = 0.78$, $p < .001$; see Figure 4). Post hoc tests showed that the semantically processed stimuli were recognized better than the studied ($p < .001$). Also, more new stimuli were endorsed correctly compared to the studied items ($p < .001$). No such difference was found between the semantically processed and the new stimuli ($p > .780$). Moreover, neither treatment ($F[1,19] = 0.02$, $\eta p^2 = 0.01$, $p > .964$) nor the interaction term treatment × stimulus type was statistically meaningful. ($F[2,38] = 0.07$, $\eta p^2 = 0.01$, $p < .934$).

The analyses of the signal detection derived measures of the non-word stimuli are presented in Table 5.

The analyses performed on the A′ scores resulted in a significant main effect of stimulus type ($F[1,19] = 41.19$, $\eta p^2 = 0.68$, $p < .001$; see Table 5). Post hoc tests showed that the participants could discriminate

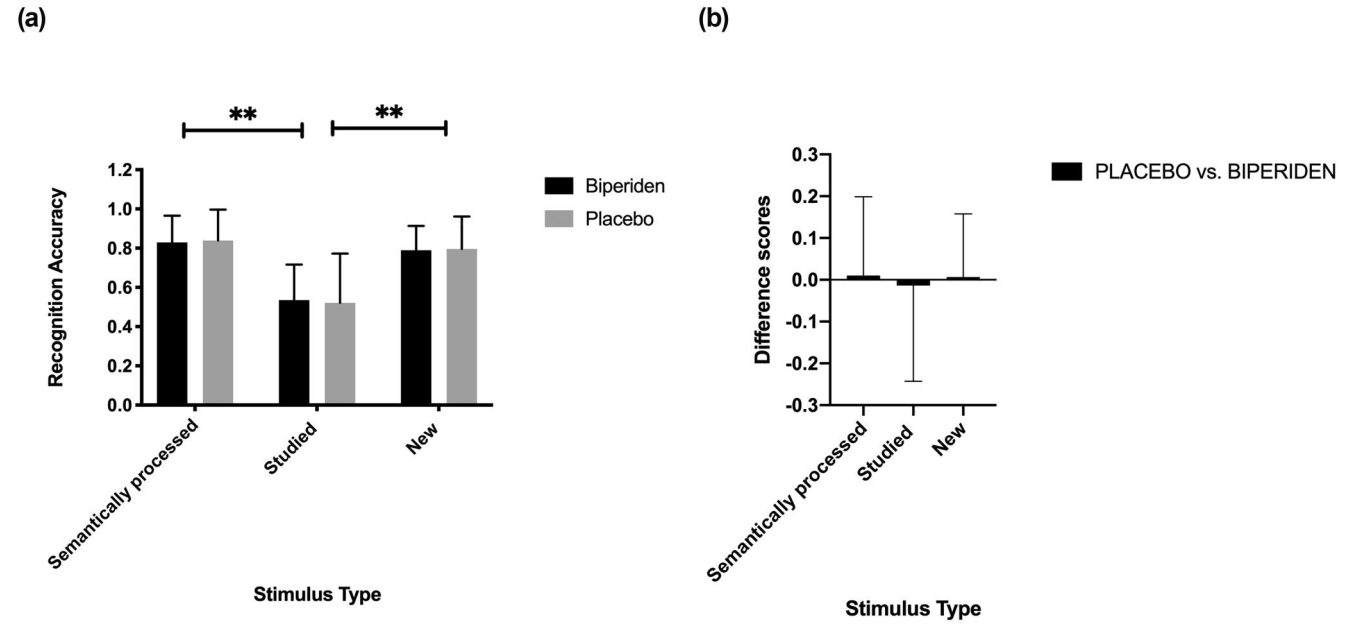

FIGURE 4 Recognition accuracy of the non-words according to treatment and stimulus type. The bars represent the means with the standard deviations. (a) Stimulus type effects shown as the proportion of the correct responses: hit rates for the semantically processed and the studied, and correct rejection rates for the new abstract figures after placebo and biperiden treatment. (b) Treatment effects depicted as the difference scores per stimulus type (semantically processed, studied, and new). $^{**}p < .001$

the semantically processed items more easily than the studied ($p < .001$). Finally, neither the treatment × stimulus type interaction ($F[1,19] = 0.04, \eta p^2 = 0.02, p > .842$; see Table 5) nor treatment was found to be significant ($F[1,19] = 0.02, \eta p^2 = 0.01, p > .903$).

3.2.2 | Reaction time data

The analyses yielded a main effect of stimulus type ($F[2,18] = 4.45, \eta p^2 = 0.33, p < .027$; see Table 6). Post hoc tests revealed that reactions to the semantically processed items were faster compared to the new ones ($p < .045$). Finally, neither treatment ($F[1,19] = 2.64, \eta p^2 = 0.12, p > .121$) nor the interaction term treatment × stimulus type was statistically meaningful ($F[2,18] = 0.35, \eta p^2 = 0.01, p > .966$).

3.3 | Complaints and POMS

The analyses did not result in any significant treatment effects for the neurovegetative complaints and the POMS (all associated t values < 1.37, $p > .330$; t values < 1.61, $p > .123$, respectively; see Table 7). Also, no further complaints other than listed in the questionnaire were mentioned. There were no adverse events found.

4 | DISCUSSION AND CONCLUSIONS

The present study aimed to examine whether BIP could model the recognition memory impairment as seen in healthy aging using an old/new recognition paradigm with abstract figures and non-words. The results show that BIP impaired the correct recognition and slowed the abstract figures' reaction times. Interestingly, BIP only impaired the recognition of the drawn (deeply memorized and repeated items relying on strong memory) and studied (shallowly memorized and not repeated items relying on weak memory) figures but not the correct identification of the new abstract figures. Furthermore, the processing of the non-words was not affected by BIP treatment.

Based on the aging literature, we expected that BIP treatment would not affect the overall recognition performance of the drawn and studied (old) stimuli. However, the current data showed that the studied abstract figures were less well recognized after BIP treatment. However, since the drug only affected the processing of the abstract

TABLE 5 Means and standard deviations of the signal-detection measures during the recognition performance of the non-words (semantically processed, studied, and new) after placebo and biperiden

Non-words			
Stimulus type	**Parameters**	**Placebo**	**Biperiden**
Semantically processed	HR	0.84 (0.16)*	0.83 (0.14)*
	A′	0.68 (0.11)*	0.68 (0.11)*
Weak	HR	0.52 (0.25)	0.54 (0.18)
	A′	0.57 (0.17)	0.56 (0.07)
New	CRR	0.80 (0.17)*	0.79 (0.12)*

Abbreviations: A', discriminability index; CRR, correct rejection rate; HR, hit rate.

Different from studied stimuli: $^{*}p < 0.001$.

TABLE 6 Median reaction times (middle 50% range; in milliseconds), and their corresponding first and third interquartile ranges in response to the non-words (semantically processed, studied and new) after placebo and biperiden treatment

Non-words		
Stimulus-type	**Placebo**	**Biperiden**
Semantically processed	628 (592–682)*	624 (587–648)*
Studied	650 (552–713)	634 (596–685)
New	698 (627–762)	669 (589–727)

Different from the new stimuli: $^*p < 0.05$.

TABLE 7 Mean difference scores as change from baseline (standard deviations) for the questionnaire data. Negative numbers indicate a decrease and positive numbers indicate an increase in the subjective feeling

	Biperiden	Placebo
Profile of mood states		
Depression	3.78 (6.67)	1.83 (6.37)
Tension	0.9 (2.63)	−0.65 (3.22)
Aggression	−0.15 (2.03)	−0.10 (1.40)
Fatigue	0.75 (2.53)	0.95 (2.69)
Vigor	4.85 (7.21)	3.35 (5.59)
Neurovegetative effects		
Headache	0.25 (0.55)	0.10 (0.55)
Sleepiness	0.60 (1.14)	0.45 (1.00)
Dizziness	0.50 (1.00)	0.50 (1.00)
Nausea	0.10 (0.31)	0.10 (0.31)
Dry mouth	0.30 (1.17)	0.60 (1.05)
Fatigue	0.55 (0.76)	0.50 (0.69)
Blurred vision	0.20 (0.83)	0.40 (0.75)
Drowsiness	0.55 (1.15)	0.65 (1.09)

figures, it is possible that the effects were related to a response bias. Namely, we detected an "old" response bias in the PLA session but not in the BIP session. Therefore, the response bias may underlie the observed drug effects on recognition memory. Further, although it was expected that BIP would decrease the discriminability index (A′) of the drawn/semantically processed and studied items, the current data did not show this impairment for either the abstract figures or the non-words. However, as expected, BIP prolonged the reaction times when responding to the drawn and the studied abstract figures. Taken together, the effects of BIP did not fully model the typical age-related deficits in recognition performance.

The finding that BIP did not affect the recognition performance of the non-words is somewhat unexpected. The treatment effects were dependent on the type of stimulus used. It could be argued that the recognition performance of the abstract pictures was better than the non-words and that the high performance is more sensitive to treatment effects. However, the performance of the non-words was about 80% correct, which can also be considered relatively high. Moreover, the strongest treatment effects for the abstract figures were found for the studied stimuli. Here, the recognition performance was about 70% correct. Therefore, the lack of treatment effects for the non-words cannot be attributed to recognition performance level.

The lack of effect for the non-words may also be explained based on an age-related difference in the use of pre-existing semantic knowledge (Badham et al., 2016; de Chastelaine et al., 2017; Fraundorf et al., 2019). Belleville et al. (2011) tested the discrimination performance of existing words versus pseudowords. They applied a two-phase study-recognition memory paradigm in young, healthy elderly, and MCI patients. Their results showed that the healthy elderly were impaired in recognizing existing words but that the performance on the pseudowords was not affected. If aging does not affect the recognition of non-words, the current data may not dismiss the notion that BIP could be a model for recognition deficits in aging. It should be noted that in the study of Belleville et al., pseudowords were only presented once, and no deep processing took place. In the current study, the non-words were deeply processed and repeated, which would make them more familiar than the pseudowords in the Belleville et al. study. Finally, it should be mentioned that BIP (2 mg) decreased correct recognition of words in the verbal learning task (Wezenberg et al., 2005). Although this is another recognition task using existing words, these data suggest that BIP could impair word recognition as seen in aging. Further studies are indicated in which the effects of BIP on the familiarity of words are tested.

The elderly often have difficulties identifying new items correctly when the old items are perceived as insufficiently distinct (Dodson et al., 2007; Fraundorf et al., 2019; Gallo et al., 2007). Consequently, new items are identified as "old" in recognition tasks (i.e., more false alarms; Gallo et al., 2007; Kroll et al., 1996). The stimuli in the current experiment were pre-experimentally unfamiliar, which theoretically could make their discrimination more difficult than the pre-experimentally known items. Indeed, several empirical studies have shown that memory is worse for pre-experimentally unknown versus known items, such as unfamiliar versus familiar symbols (Cycowicz & Friedman, 2007), words versus non-words (Belleville et al., 2011; Gardiner & Java, 1990). In agreement with these findings, BIP should decrease the number of correctly recognized new stimuli (abstract pictures and non-words). However, this was not observed in the current study, which further undermines the notion that BIP models recognition deficits in aging.

The drug-induced impairment in reaction times to the abstract figures complies with the well-documented age-dependent cognitive slowing (Levin et al., 1992; Salthouse, 1996; van Hooren et al., 2007). A decrease in response times after BIP has also been observed in other tasks in previous results (Sambeth et al., 2015; Silver & Geraisy, 1995; Wezenberg et al., 2005). In addition, pictures are represented as integrated patterns (Rajaram, 1996), and their processing requires additional allocation of attentional resources, which can

slow down reactions (Noldy et al., 1990). If this was true, then BIP might have affected attention. However, this seems unlikely considering that participants did not report sedation in the present study.

Furthermore, our findings align with previous research. Firstly, the memory strength manipulation showed a clear difference between the deeply and shallowly processed stimuli (Hulstijn, 1997; Paivio & Desrochers, 1981; Solso, 1995). Secondly, in the PLA condition, previous behavioral findings using this paradigm were replicated (Toth et al., 2021). Namely, the correct identification of the new abstract figures and non-words was superior to old item recognition when they were merely studied and not repeated, but not when they were drawn or semantically processed. Finally, as in previous studies, 4 mg BIP did not cause any adverse effects as measured by the POMS.

In closing, although BIP has been found to mimic an episodic memory impairment in young, healthy volunteers, the current data do not indicate that BIP can adequately model typical age-related deficits in recognition performance of abstract figures and non-words.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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